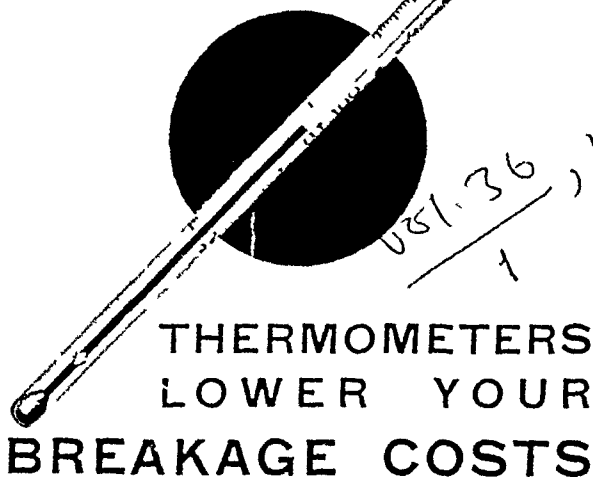




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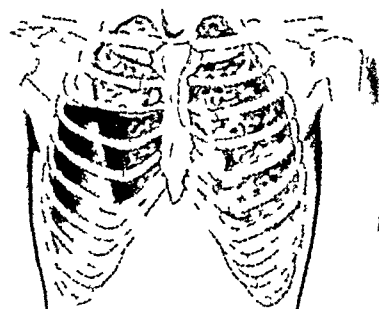
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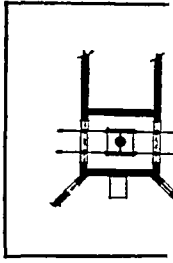
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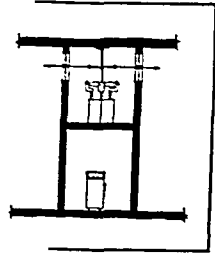
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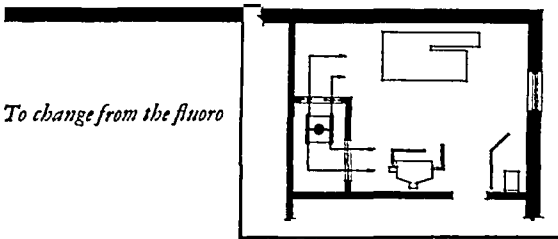
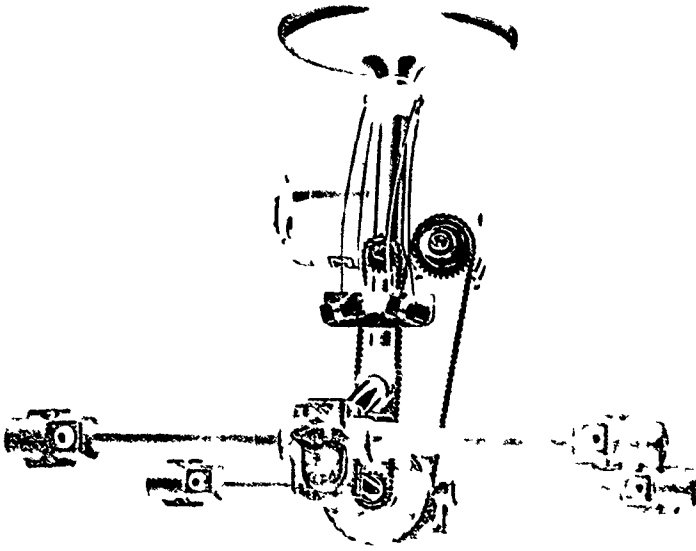




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# CONTENTS

LEACH, EUGENE R. The Clinic, the Laboratory and the Field	1
BASWORTH, JOHN B. LITTLE, JOHN AND CLIP, JOHN I. Ulcerative Tuberculous Tracheobronchitis	8
ANDERSON, PAUL M. Bronchiectasis	16
PORTER, F. I. AND GOLDMAN, WYLLIE H. The Size of the Heart in Pulmonary Tuberculosis	82
KELLY, THOMAS, CAMERON, ROSENBURG, HAROLD A. AND PAUL, WILLIAM H. Tuberculin Vaccination Produced by Parenteral BCG Vaccination	90
DONN, MORRIS. Treatment of Pulmonary Tuberculosis with Gold Sodium Thio-sulphate	100
LINDLEY, HAROLD GUYER AND WARDLAW, BURNHAM H. Pneumoperitoneum in Treatment of Pulmonary Tuberculosis	111
MALME, JESSE. The Effect of Splenectomy on Tuberculosis Infection in Mice	119
CLEGG, MORRIS AND COHEN, MAURICE I. The Certain Diagnosis of Tuberculosis	126
KRUSE, ALBERT. Index	133

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# THE CLINIC, THE LABORATORY AND THE FIELD

The Address of the President<sup>1</sup>

ESMOND R. LONG<sup>2</sup>

Uniquely in the control of human disease the campaign against tuberculosis combines the three powerful forces of medical skill, exact study by technical device, and a far flung organization for reaching the mass of people and bestowing the benefits of modern science

These forces, or rather their domain, may briefly be designated the clinic, the laboratory and the field. And in this short list is comprehended not only the modern attack on the disease, but in remarkable chronological succession the whole history of tuberculosis

So logical does this combination of forces seem to us to-day, allied as we are in the antituberculosis campaign, and so effective does it appear to our close-range view, that it is difficult to imagine a successful war upon this disease without it. But in the long course of medical history the one has slowly waited for another, and it is only fifty years since the tremendous power of the third was added to the spectacular yet less effective advance of the first two

In no ailment has the cultivation of what we may call the field been as important as in tuberculosis. Medical history furnishes many examples of quick control of disease through the combined operation of the clinic and the laboratory. In smallpox and diphtheria after centuries of clinical understanding the laboratory furnished a rapid short cut to mastery. The public required persuasion, to be sure, before preventive methods became general, but no such elaborate organization needed to be built as has been the case with tuberculosis. Neither the laboratory nor the clinic has furnished a short cut to its control. In the extraordinary check of typhoid fever, once a wide spread scourge and now a rarity, the laboratory, coming to the aid of the clinic, furnished a ready basis for effective sanitary engineering, while the bulk of the population remained ignorant of the measures taken for their protection. The

<sup>1</sup>Delivered at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, May 31, 1937

<sup>2</sup>The Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania

water that spreads typhoid fever is subject to mechanical supervision, the air through which tuberculosis is spread unfortunately is not. Other comparisons might be made, but it is enough to say that the control of tuberculosis through intensive cultivation of the field is without parallel in the attack upon sickness.

Medical familiarity with tuberculosis is almost as old as any medical writing. The clinical descriptions of the Hippocratic school of physicians leave no doubt of the character of the disease in ancient times. The illness was clearly set apart, on the basis of symptoms, as a clinical entity, and treated according to the best thought of the time. But how common it was, how important in the total list of diseases, there is no direct report to show. By an indirect approach we can make some guess, as we know something of the manner of living, the degree of crowding, the amount of malnutrition and other environmental factors in the life of ancient peoples. Some hint of a demographic outlook, some consciousness, so to speak, of the field, is to be seen in ancient correlation with varying climatic states, but the field was practically uncultivated, and was to stay so for many centuries.

Clinical practice remained the sole element in the conscious fight against tuberculosis until the laboratory science of pathology brought fresh understanding. This lengthy period from the time when the well-known symptoms of advanced illness first made the diagnosis until the day when experience at the necropsy table gave the disease a new definition has been aptly termed the period "from consumption to tuberculosis."

After the seventeenth century the clinic and the laboratory were allied. It is true, the laboratory science of tuberculosis had its vague beginnings long before this, even in Hippocrates's own time, when significant characteristics of the sputum of consumptives were recorded. But the deliberate opening of the human body, the painstaking objective study, and final identification of symptoms and organic visceral change, by the seventeenth century anatomists, were the first great strides, and perhaps the greatest steps, in the understanding of tuberculosis.

Yet it cannot be said that this laboratory contribution to the knowledge of the clinic had any immediate effect on the control of tuberculosis. To be sure it brought the disease out of the dark into the open of new investigation, but no physician of the time of Sylvius and Morton could attack tuberculosis the better because he knew his patients' symptoms came from cheesy degeneration of the lungs. Not that the new dis-

covery had no effect on medical practice Sylvius himself promptly incorporated his anatomical findings in his philosophical concept of the disorder, and treated the latter accordingly, but the concept was wrong, and the treatment presumably worthless also For the rank and file in medical practice the therapy of tuberculosis was empiric, as it is to large extent to-day, and the horseback riding of Sydenham was as effective a mode of treatment as any of the supposedly refined procedures based on anatomical understanding

But whether the combination was at once effective in the clinic or not, the clinic and the laboratory were fused for all the future The long chain of technical investigation that was to lead from the identification of the multitude of forms of tuberculosis to recognition of its specific cause and to perfected means of diagnosis was begun The great advances in tuberculosis from the end of the seventeenth to the beginning of the nineteenth century were in the laboratory For a century laboratory progress was to be confined to the gathering experience at the necropsy table Out of the opening of thousands of bodies, culminating in the brilliant synthesis of knowledge by Laennec, came understanding of the whole anatomical course of tuberculosis from the smallest tubercle to fatal cavities and pneumonic consolidation of the lungs In the identification of phthisis and scrofula the laboratory had vastly widened the field of tuberculosis, for scrofula for a thousand years had been almost the commonest serious ailment of mankind, and phthisis was carrying off one-fifth of the population The laboratory made it apparent that tuberculosis was the most widespread of all chronic diseases, and it could be truly said then, as was said later, that "everyone has a little tuberculosis"

At the opening of the nineteenth century the tuberculosis clinic was rejuvenated by epoch-marking developments in diagnosis Just as the period of greatest anatomical progress was closing, a period of extraordinary clinical advance was beginning And remarkably, Laennec, who had so much to do with settling anatomical dispute, had a major part in the new development If the century before Laennec was the century of impressive pathological unfolding, the century following was one of notable increase in knowledge through the art of physical diagnosis Delicate touch and listening opened a new world to the clinician, who for centuries had stood helpless, waiting for unmistakable symptoms to develop With physical diagnosis, for the first time, came the early case

In the middle of the nineteenth century dramatic developments, wholly unrelated, occurred in both the clinic and the laboratory of tuberculosis. The clinical innovation was the sanatorium. Coming at the close of the exercise period in the treatment of tuberculosis, and itself devised originally as a school for exercise, the sanatorium later developed into exactly the opposite, a place for recovery through rest. For some decades it was an uncomplicated clinical experiment. The early sanatoria had no laboratories, as there was nothing to investigate, except the body after death, and there was no attempt to reach the masses. As late as 1908 Osler wrote, "At present we are in the sanatorium phase of treatment. But the disease is so widely prevalent that we can never hope to place sanatorium treatment at the disposal of more than a very small percentage of patients." And yet in less than twenty years health officers engaged in the control of tuberculosis had come to accept a requirement of one sanatorium bed per annual death from tuberculosis in any community as the minimum standard for adequate control of the disease. Within a few years, experienced men in the field had set two beds per annual death as a better goal. In 1908 only 12,000 sanatorium beds were available for tuberculous patients, but in 1928 the number was nearly 70,000.

In those two decades sanatoria, springing up throughout the country, had proved effective demonstration centres, and an awakened sense of public health responsibility was rapidly making them available not to the fortunate few, but to the population at large. The sanatorium had reached the field. To-day there are 95,000 beds for the treatment of tuberculosis in the United States.

Coincident, as I have said, with the first operation of sanatoria, came two laboratory advances in the understanding of tuberculosis, both of them to be of the utmost practical importance. The first was a simple extension from the gross to the minute anatomy of tuberculosis. The microscope and the microtome, and soon the development of tissue stains, greatly refined the understanding of tuberculosis, which had begun two centuries before when coarse cheesy tubercles were first recognized as distinctive. The Cellular Pathology was giving new breath of life to all medicine, and the science of tuberculosis had its full share of advance with the new knowledge and technique.

The other development was the demonstration that tuberculosis is an infectious disease. The early inoculation experience proving its transmissibility was followed by Koch's actual demonstration of the cause

The laboratory had become "practical" at last, for here was a development which, it would seem, the clinic could not afford to ignore. Strangely enough, it did ignore it for a time, probably because the laboratory itself had proved tuberculosis so nearly universal, and inevitable, that the recognition of its cause seemed at first of more academic than practical significance.

But measured against the whole history of tuberculosis the lag between the discovery of the tubercle bacillus and the application of the discovery in preventive medicine was infinitesimal. Indeed but a few years later, just fifty years ago, to be exact, the rational application of all facts at hand began.

Up to this time, although tuberculosis had long been decreasing through the operation of certain social causes, medical science could not claim, either through the clinic or the laboratory, much share in mass control of the disease. With the advent of the public health movement the share of medicine in the conquest became unmistakable.

In 1887 Sir Robert Philip established in Edinburgh the original dispensary for attack upon tuberculosis. This was soon followed, in New York City, by the first attempt at comprehensive public health control of the disease. And from these two beginnings has grown a far reaching campaign that today seems to follow the only logical course. The dispensary was the precursor of the present elaborate system of ambulant treatment, field nursing, case finding and provision for care of patients discovered, a system that has brought into antituberculosis work not only the clinician, not only the laboratory investigator and technician, but all the forces of public health, including a trained nursing and social service personnel and a vast army of lay workers who have succeeded in popularizing the subject and greatly facilitated the work of the technically trained forces.

Two thousand years of the clinic, three hundred of the laboratory and fifty years of this intensive cultivation of the field! To the first two we may credit the understanding of tuberculosis, but to the last we may indeed look for its ultimate practical eradication.

We are now, after long years, at a point where the three effective forces in the campaign are advancing simultaneously, and dependent on each other. If it is true that the field could make no progress whatsoever without the clinic and the laboratory, it is equally a fact that the clinic and laboratory without the field forces would only dent the mass problem, as they did in the past. Within recent decades the laboratory has



provided the clinic with the X-ray and the tuberculin test, but without the case-finding organization effected by the field personnel these two powerful weapons in the antituberculosis campaign would have a relatively restricted application. Within recent years, too, the clinic has introduced new and unusually successful methods for the treatment of tuberculosis, but, without the extensive dispensary, hospital and sanatorium facilities brought into existence through a well calculated propagandizing of the field, the benefits of this treatment would reach but a few of the enormous numbers favored at present.

In America this effective combination has resulted from thirty years work by the National Tuberculosis Association. The development of a wise unified plan is evident in the long series of annual meetings of the Association, each with its scientific sessions, representing the clinic and the laboratory, and its sessions for social work and administration, representing the field. The more recent system of combined section meetings testifies to a growing appreciation of the fact that these are not separate departments in the antituberculosis campaign, but a collection of vital interests to be cultivated together.

No one of these forces can afford to stand still. Each has the job of technical application of present understanding, but for each there is a road forward. We are essentially a research organization. For the clinic the history of tuberculosis is a long story of changing therapy. There is no reason to suppose that we have at last reached the top. Collapse therapy is the triumph of the moment, but we are too close to recent developments to know whether it is the solution or a simple phase of advancement in treatment of the disease. Continued investigation is essential. The laboratory in tuberculosis must keep pace with general scientific advance, and need not be deterred by any criticism of impracticality. Use will always be found for what is proved to be true. The first laboratory advance, anatomical understanding, probably in the beginning seemed of mere theoretical interest to the clinic, but to-day's indispensable X-ray film would be meaningless without the laboratory-built understanding of the lesions for which the shadows stand.

For the field remains the hardest task of all. Its work will continue to be the development of machinery for finding the cases of tuberculosis, and by education, legislation and otherwise to make sure of their adequate care and thereby prevent spread of the disease. This is difficult enough, but a further concern lies in the fact that our mass methods have outmoded some of the old established methods of individual medical

practice The field operation of antituberculosis measures, essential, as we have seen, to mass control of the disease, has pioneered in new procedures in preventive medicine We are at a point where leadership in administration and social planning must pioneer further to fit the new harmoniously to the old In all probability at some future time—and it may be decades hence—the law of diminishing returns will operate so that the need for an elaborate voluntary organization to check tuberculosis will be past Presumably, however, there will always be a residuum of tuberculosis, just as there is of typhoid fever and other nearly conquered diseases The prevention of spread from this residuum must be recognized as a continuing public health problem of importance The ensurance of an effective, permanent official program to keep this residuum at minimal proportions, is, as conceived by the Founders, the final responsibility of our field organization

# ULCERATIVE TUBERCULOUS TRACHEOBRONCHITIS<sup>1</sup>

JOHN B BARNWELL, JOHN LITTIG AND JOHN E CULP

## INTRODUCTION

In spite of a definite symptom complex, tuberculosis of the airway below the larynx has only recently been recognized by the clinician. Like laryngeal tuberculosis, it adds gravity to the prognosis, yet it shares in none of the benefits of modern collapse therapy. Two factors are chiefly responsible for having kept obscure this serious complication of pulmonary tuberculosis. First, it is inaccessible to the usual methods of examination, and second, the routine necropsy technique of examining the thoracic viscera is not directed toward the detection of its frequency.

Clinical contributions to the literature are all of recent date. Various types of obstructive lesions of the trachea, main and lobar bronchi, occurring as a complication in pulmonary tuberculosis, are reported. The following are the main contributions in the American literature.

Schonwald (1), Clerf (2), McConkey (3), Myerson (6), Tucker (7), Eloesser (8) and Coryllos (9) have recognized and described bronchial complications under the following headings: (1) ulcerative lesions, (2) stenosing fibrotic lesions, (3) caseous thrombus, (4) fibrinous plug, (5) tuberculoma and (6) tuberculous granulation tissue, all causing various degrees of stenosis and obstruction, and giving rise to definite clinical signs and symptoms. Lord (10), Hoover (11), McPhedran (12), and Norris and Landis (13) have referred to tuberculosis of the trachea and bronchi, and Jackson (14) has described its endoscopic appearance. Eloesser, in addition, describes extramural lesions and a diffuse stenosis of the smaller bronchi (obliterative bronchiolitis).

In the broad group of tracheal and bronchial complications represented in the literature, there are two common features: (1) tuberculous aetiology and (2) tracheal or bronchial obstruction. In our experience, no generalization could be made if all the cases presenting these two common features were grouped under one head. The one subgroup which most nearly fitted into or could be classified as a clinical entity were

<sup>1</sup> From the Department of Internal Medicine, Medical School, University of Michigan, Ann Arbor, Michigan.

those with ulcerations. These cases with ulcerations frequently have features in common with other groups, namely extrinsic pressure, cicatricial stenosis and tuberculoma. For clarification of both the diagnosis and the clinical picture, we have chosen to present at this time only those with tuberculous ulcerations.

Our interest in this complication was aroused by our observation of several patients whose symptoms were unexplained until the bronchoscopist found tuberculous ulcers of the mucosa of the trachea and bronchi. Since this observation in 1929, awareness of the possibility has led to an antemortem clinical diagnosis in nine cases of tuberculous ulcerations of these structures. These observations have stimulated autopsy studies to be reported elsewhere (Bugher, Littig and Culp (16)).

We have selected for this report six typical cases of ulcerative tuberculous tracheobronchitis seen at the University of Michigan Hospital in the past seven years, all of which were recognized by the clinician first and later the clinical diagnosis was verified by the bronchoscopist. Other cases with a clinical diagnosis, but in which no bronchoscopy was obtained, are not included in this report.

#### CASE HISTORIES

*1* No. 205796, M. P., white, woman, age 29, was admitted November 6, 1928, with a history suggesting a catarrhal onset of pulmonary tuberculosis extending over a four-year period. The history was unusual only because of definite shortness of breath on moderate exertion. Examination of the chest at this time revealed impaired resonance over the upper third of the right lung, and transient rales over the left, localized beneath the left clavicle. The sputum contained tubercle bacilli, and the admission X-ray examination, dated November 6, 1928, (figure 1A) showed soft blotchy shadows in the upper left lung field, suggestive of tuberculosis. A dense triangular shadow was interpreted as representing atelectasis of the right upper lobe. This shadow of atelectasis was not present in a film taken in August, 1928, three months before admission, but in its place was the moderately advanced mottling of this lobe.

Ten weeks later, January 21, 1929, the dense shadow on the right had again been replaced by the picture of August, 1928. The clinical course was considered satisfactory, cough less, sputum markedly decreased, and a gain of nine pounds in weight. In June, 1929, the patient had an attack, characterized by a severe paroxysm of coughing, dyspnoea, and cyanosis. At this time a rough expiratory sound was audible throughout both lung fields. X-rays of May 10 and June 27, 1929, showed no change other than slight increase of the shadows in the upper left lung.

Fig 1A

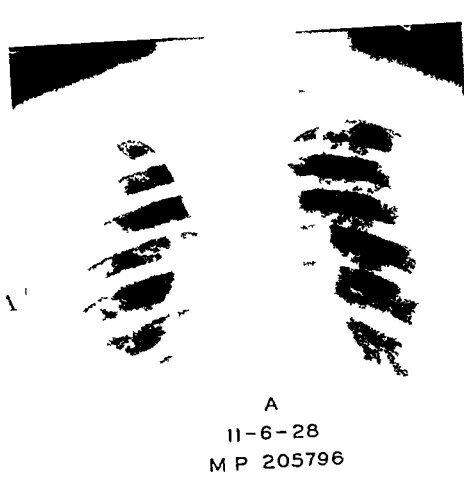


Fig 1B

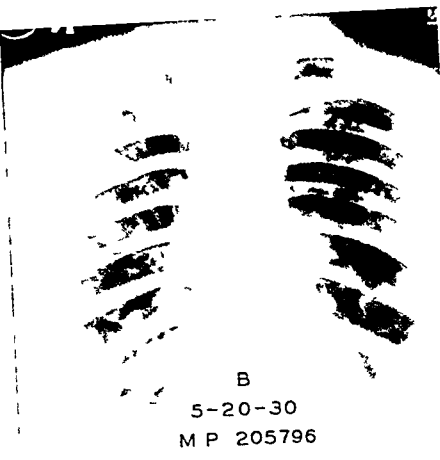


Fig 1C

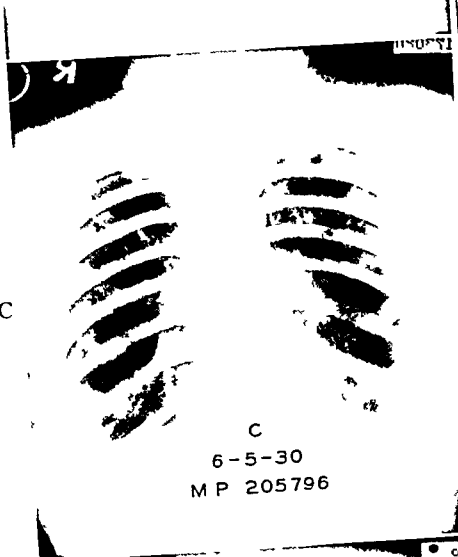


Fig 1D



Fig 1E

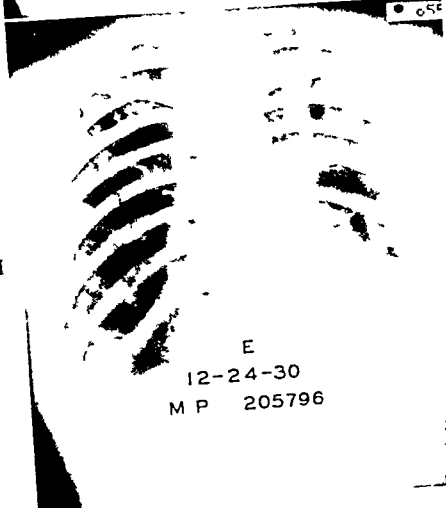
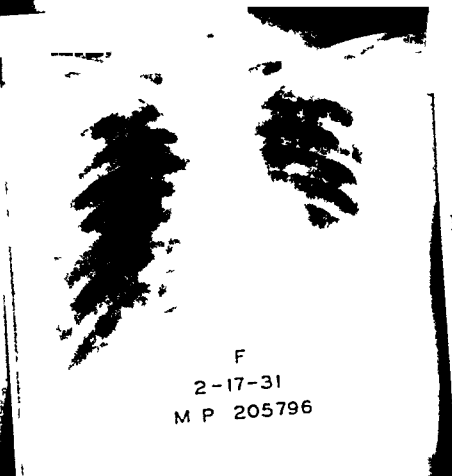


Fig 1F



In August, 1929 atelectasis was still absent and slight clearing was noted in both lung fields. However the shadow of atelectasis reappeared in the film of November 5, 1929, and persisted in the X-ray of January 20, 1930, but appeared smaller on each examination. The shadow representing atelectasis was again absent from the X-rays of March 7, March 11, and May 20, 1930, (figure 1B) but reappeared smaller than ever in the film of June 5, 1930, (figure 1C) at which time there was an increase of shadows in the third left anterior interspace. A comparison of figure 1A with figure 1C represents the very slight increase of shadow developing in nineteen months of conservative treatment, six months on a Bradford frame for suspected Pott's disease, the remainder at complete bedrest.

During the last twelve months of this period, the patient continued to experience periodic "asthma-like" attacks, variable in frequency and severity,

#### *Case I*

FIG 1A Atelectasis of right upper lobe on admission with no shift of trachea, mediastinum or diaphragm.

FIG 1B Right upper lobe inflated. Note the mottling in the right first anterior interspace.

FIG 1C The result of nineteen months bed rest. The right upper lobe is again atelectatic after repeated re-expansion and is now shrunken. The mottling seen in the right first anterior interspace in B, which 16 days before, has now disappeared into the atelectatic upper lobe. In spite of the small size of this lobe there is no displacement of the trachea or mediastinum or elevation of the diaphragm. The slight increase of shadow in the left midlung represents the only change from the condition seen in A.

FIG 1D Six weeks following bronchoscopy and biopsy. Mottled right upper lobe again expanded. Beginning of rapid increases in the left lung.

FIG 1E Four months continued progression in the left lung.

FIG 1F Twelve days after the second bronchoscopy, six weeks before death. Beginning involvement right base and further extension on the left. This shadow at the left base suggests atelectasis, but by the time of autopsy there was tuberculous pneumonia in this area.

associated with paroxysms of coughing. The attacks were very alarming and the respiratory distress tremendous, they were separated by periods of apparent well-being, except for occasional rises in temperature to 101°F. Rhonchi were palpable over both lungs, hoarseness had become a symptom, an ulcer was present in the larynx (November 25, 1929).

June 19, 1930, the patient was bronchoscoped, (Dr Furstenberg) the right bronchus being grossly ulcerated four centimeters below the carina. Large masses of granulation tissue extended from the ulcerated area into the bronchial lumen. A biopsy was taken from the ulcerated area and reported as caseous tuberculosis.

It may be noted that up to this time the atelectasis appeared and disappeared at intervals. X-rays, frequently interspersed with fluoroscopic observations, failed to determine any definite relation between the appearance of the atelectasis and the occurrence of symptoms. Although no observations

were made during an acute attack, it may be said that the atelectasis was both present and absent during periods of comparative comfort. When the shadow was present, all of the previous mottling disappeared, indicating that the involvement was principally confined to the lobe which became atelectatic. August 5, 1930, the X-ray (figure 1D) showed the final disappearance of the atelectasis and the beginning of rapid increases in shadows in the left lung, which continued through the X-rays of October 23, 1930, and December 24, 1930 (figure 1E).

February 5, 1931, a second bronchoscopy was done (Mr. Nelson), the lumen of the trachea was reported reduced, and the mucosa appeared oedematous, no tracheal rings could be seen. The mucosa of both main bronchi was in a similar state, with narrowing of the lumen, but without ulceration.

The symptoms were greatly aggravated following this procedure, a low tracheotomy was performed (Dr. Alexander), suction was established, but without definitely influencing the patient's condition. Twelve days after the second bronchoscopy, an X-ray of the chest dated February 17, 1931 (figure 1F) revealed a continuation of increases on the left and the beginning of massive changes on the right, both of which were continued in the X-rays of April 1, 1931, taken three days before death. Attention is called to the marked and rapid increase in X-ray shadows following the first bronchoscopy, at which time a biopsy was taken, (figure 1C before bronchoscopy), and (figures 1D & 1E after bronchoscopy), and exaggerated after the second bronchoscopy (figure 1F). This is especially noteworthy when viewed in the light of the twenty months preceding bronchoscopy, when little parenchymal change was observed (figures 1A & 1C).

Death followed six years and seven months after the onset of tuberculosis, twenty-two months after the first attack of dyspnoea, twenty-nine months after the beginning of conservative treatment, ten months after the first bronchoscopy and two months after the second bronchoscopy.

*Autopsy* (Dr. Weller). The right upper lobe which had been the site of intermittent atelectases, but which had been reexpanded for eight months before death, was grayish in color and emphysematous in appearance. On cut section, it showed emphysema and occasional small healed tubercles. The bronchus to this lobe was apparently constricted by enlarged glands surrounding the bifurcation of the trachea. The bronchi were generally filled with purulent material, but chiefly on the left. The mucosa was swollen, but no ulcer was seen. The right lower lobe and the two left lobes contained areas of caseous pneumonia, beginning cavitation and atelectasis.

2 No 174084, T. S., white, woman, age 43 years, was admitted July 1, 1927, with complaints of weakness and "wheezing in the upper left lung." Aside from slight cough, afternoon fever, and the presence of tuberculous infection

in her family, her history was noncontributory. Coarse râles were audible in the upper left anterior lung. The tuberculin test was positive, but the sputum contained no tubercle bacilli. X-rays in July, August and October, 1927, showed a shadow off the left border of the heart that was not diagnostic of tuberculosis but that increased in size in three months' observation.

The two year course at home finally ended in admission to the Michigan State Sanatorium. There the sputum contained tubercle bacilli and there was a daily febrile reaction. The sanatorium admission X-ray, July 31, 1929 (figure 2A)<sup>2</sup>, showed a slight decrease in the shadow off the left border of the heart since October, 1927. The next X-ray, December 4, 1929 (figure 2B), showed the trachea, mediastinum and heart retracted to the left and a homogenous shadow occupying the left base up to the third anterior rib. This shadow is now interpreted as atelectasis, but then as pneumonia. The left lung was collapsed by pneumothorax induced February 15, 1930, and an X-ray two days later showed some aeration in the previously atelectatic left lower lobe, but atelectasis now of the left upper lobe though the total collapse was no more than 20 per cent. The next X-ray, April 3, 1930 (figure 2C), shows atelectasis of the left lung and the beginning contraction of this lung which progressed to the degree seen on October 4, 1932 (figure 2D). This progressive contraction of the left lung was little influenced by paralysis of the left diaphragm, May 30, 1930, and cauterization of several adhesions, January 17, 1931 (Dr Alexander). Both operations were indicated by the continued presence of tubercle bacilli in the sputum in spite of the degree of collapse already achieved.

During the fall of 1930, four months before thoracoscopy, she had her first attack of dyspnoea and difficulty in both respiratory phases. The distress increased following pneumothorax refills. Attacks simulating asthma followed, consisting of paroxysmal cough, dyspnoea, and expectoration of thick, tenacious sputum. These attacks, which were becoming more frequent and severe, were described as coming on suddenly, producing dyspnoea, slight cyanosis, and a loud stertorous rattle, audible some distance from the patient.

Small refills were continued on the left but, due to increasing respiratory distress, she was transferred to the University Hospital in November, 1932, for investigation of the tracheobronchial tree. Physical examination at this time showed an inspiratory heave, harsh breath sounds beneath the angle of the right scapula, and in the left midaxilla "respiratory grunts and creakings," especially affecting the inspiratory phase, and suggesting to the examiner the possibility of bronchial obstruction.

Her course was gradually downhill, the attacks were not relieved by discontinuing the pneumothorax refills or by aspiration of air, and the lung re-

<sup>2</sup> Through the courtesy and kindness of Dr. George Leshe, Medical Director, Michigan State Sanatorium, Howell, Michigan, we have reproduced his films (figures 2A, B, C & D).



Fig 2A

A  
7-31-29  
TS 174084

Fig 2B

B  
12-4-29  
TS 174084

Fig 2C

C  
4-3-30  
TS 174084

Fig 2D

D  
10-4-32  
TS 174084

Fig 3

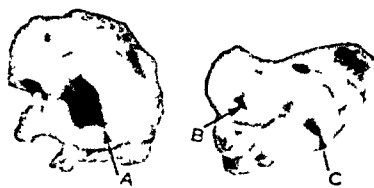
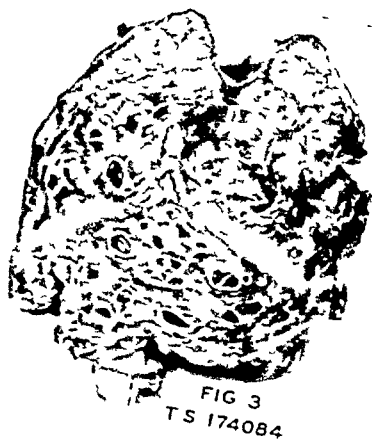


Fig 4

remained completely collapsed. Bronchoscopy (Dr. Jones) on December 30, 1932 showed a normal upper trachea. One inch above the carina, the mucosa was thickened and the lumen narrowed, a stenosis being present. This took the form of a nonulcerating, circular, infiltration barely admitting the large aspirating tip. The area beyond the carina would not admit the bronchoscope. Aspirated secretions were loaded with acid-fast bacilli. The situation became desperate, and a low tracheotomy (Dr. Maxwell) was performed for the purpose of inserting a long tracheotomy tube, which gave some relief, and to minimize the trauma of the six bronchoscopies (Drs. Furstenberg, Canfield, Maxwell and Beavis), necessitated during the three days before death for the removal of crusts from the bed of a large ulcer in the left main stem bronchus and the unsuccessful attempt to dilate the stenosed left bronchus.

### *Case 2*

Fig 2A Left lung shows light scattered tuberculous infiltration from apex to third anterior rib, homogeneous density off left border of heart.

Fig 2B Trachea, mediastinum and heart retracted to left. Homogeneous density at left base is probably atelectasis of lower lobe.

Fig 2C Atelectasis both left lobes six weeks following induction of pneumothorax. Heart in normal position.

Fig 2D After thirty-two months of pneumothorax. Two months before death. End of progressive retraction of left lung. Elevation of left diaphragm due to interruption of left phrenic nerve.

Fig 3 Contracted left lung, equivalent in size to the cadaver's fist. Dilated bronchi occupy large share of total cut surface.

Fig 4 Section through trachea showing irregularity of tracheal wall due to ulceration, A. Section through bifurcation shows disproportion in size of lumina of left bronchus B and right bronchus C.

Death occurred on April 1, 1933, five years and seven months after the onset of the bronchial symptoms, three and one half years following left pneumothorax and paralysis of the left hemidiaphragm, and three and one half years following the onset of acute respiratory distress.

*Autopsy* (Dr. Weller) revealed left sided pneumothorax with a completely collapsed and atelectatic left lung, equivalent in size to the cadaver's fist. It had a solid consistency and did not float in water. Longitudinal section showed the bronchi so close together that they appeared to make up about one half the tissue present (figure 3). The bronchi were markedly thickened with a rough, granular mucosa, and the lumina were filled with a thick mucoid, gelatinous material that protruded above the cut surface like well-formed molds of the bronchial lumen. The left main bronchus was markedly stenosed, being about six millimeters in diameter with a rough granular mucosa and irregularly shaped areas of ulceration (figure 4). The entire mucosal surface of the trachea was roughened and granular with diffuse ulceration and necrosis.

The right lung was uniformly emphysematous and pink except at the dependent portion of the lower lobe where it was firm to palpation and purple in color

3 No 205324, D W, white, girl of 17 years, was admitted to the University Hospital October 29, 1928, complaining of cough and pain over the left chest. The diagnosis of pulmonary tuberculosis was established on physical findings and X-rays. The first twelve months of bed-rest were attended with slight change in the X-rays, but from the thirteenth to the fifteenth month there were rapid bilateral increases. Pneumothorax was induced on the left in January, 1930, after the first finding of tubercle bacilli in the sputum. Right pneumothorax was induced in May of the same year.

The second year was somewhat more satisfactory, serial chest films showing increase in bilateral pneumothorax and evidence of clearing of the partially collapsed lungs in spite of numerous bilateral adhesions. During this period several examiners reported rhonchi that were quite distressing to the patient. In October, 1930, dyspnoea became a little more marked following refills and in December, 1930, dyspnoea was further increased as was the cough and sputum, which was occasionally blood streaked.

In October, 1931, she was transferred to the Michigan State Sanatorium with continuation of the same treatment. She did quite well until January, 1932, when weight loss, increase in cough and sputum, and difficult expectoration developed, the latter following pneumothorax refills. Removal of air from the pleural cavity occasionally gave slight relief. She was returned April 20, 1932, to the University Hospital in extreme dyspnoea and, during laryngoscopic examination (Dr Maxwell), a large inspissated plug of mucus and fibrin, one and one-half inches long, was removed from the trachea with immediate relief. She was returned to the State Sanatorium, where bilateral pneumothorax was continued. In August, 1932, she began to have attacks of rattling and stertor in the throat and expiratory difficulty. Expectoration of thick, tenacious sputum produced some relief. The respiratory distress increased, and loud tracheal rattles were audible in the patient's room. She was admitted a third time to the University Hospital, where bronchoscopy (Dr Canfield) showed a diffuse ulcerative tracheitis with narrowing of the lumen of the lower trachea and the bronchi. A biopsy of the mucosa showed caseous tuberculosis.

The attacks of dyspnoea, wheezing, cyanosis, paroxysms of coughing and expectoration of thick, tenacious sputum continued. Bronchial and bronchovesicular breathing were clearly audible on the left. Breath sounds were absent on the right, but many rales, rhonchi, and wheezes were heard in both phases of respiration. The clinical impression was obstruction to the right main bronchus. A second bronchoscopy (Dr Canfield) showed an ulcerating,

obstructing lesion in the right main bronchus, with pieces of moving slough attached to the edges. These were removed with marked symptomatic relief. The tracheal mucosa was considerably improved when compared with the examination of one month previously, patches of hyperaemia being noted, but no ulceration.

The distribution of many string-like adhesions suggested the possibility that torsion of the bronchi and their branches added to the existent respiratory difficulty. Consequently, the right pneumothorax was abandoned, resulting in rapid dissemination throughout the right lung and the development of a cavity. The left pneumothorax was continued, and, prior to again returning to the State Sanatorium, bronchoscopic examination (Dr. Canfield) was repeated. The tracheal mucosa was intact, showing only roughening, the right bronchus contained purulent discharge, the mucosa being hyperaemic, but free from crusting ulcerations as previously noted. The left bronchus appeared normal.

For eight months before final admission to the University Hospital, she noticed that the slightest exertion brought on distressing respiratory symptoms. Her sputum continued thick and tenacious, constantly containing tubercle bacilli.

The fourth bronchoscopic examination (Dr. Jones), done one month before death, showed a sclerotic, scarred mucosa, and narrowed lumen of the entire tracheobronchial tree. The lobe orifices and both stem bronchi appeared stenosed, as if by fibrosis and scarring, this being more marked on the right. No ulcerations were seen.

Her subsequent course was progressively downhill, being marked by increasing expectoration, daily fever, tachycardia and embarrassed respirations. Death occurred September 14, 1933, five years after the onset of dyspnoea and three and a half years following institution of bilateral pneumothorax. Permission for autopsy was refused.

4. No. 309768, L. H., white, woman, age 27 years, was admitted March 10, 1933, complaining of cough and "rattle in the throat." The onset was insidious with ease of fatigue and weakness antedating admission two and one-half years. A sudden attack of wheezing, diagnosed as asthma (no X-ray taken) occurred one year before admission. No subsequent wheezing occurred, but the patient was conscious of an irritation in her throat resembling a "rattle," more pronounced in the supine position. Weight loss, night sweats and cough developed two months before our first examination. On physical examination, a lag on the right, palpable and audible rhonchi in the right apex anteriorly, first to third ribs, and friction rub in the right axilla were noted. The diagnosis of pulmonary tuberculosis was based on X-ray findings, March 29, 1933, of a unilateral lesion involving the right upper lobe (figure

5A), and positive sputum April 1, 1933, a temporary paralysis of the right hemidiaphragm (Dr Haight) was done and on April 20, 1933, an X-ray (figure 5B) showed the rise of the right diaphragm and atelectasis of the right upper lobe. This effected no change in symptoms but the sputum disappeared or contained no tubercle bacilli until July when tubercle bacilli were again found.

In September, 1933, there was a definite clinical change, cough becoming more severe, and thick, tenacious sputum increasing in amount. She experienced mild respiratory distress and audible wheezing. On one occasion during a severe paroxysm of coughing, a mucous plug the size of the tip of the little

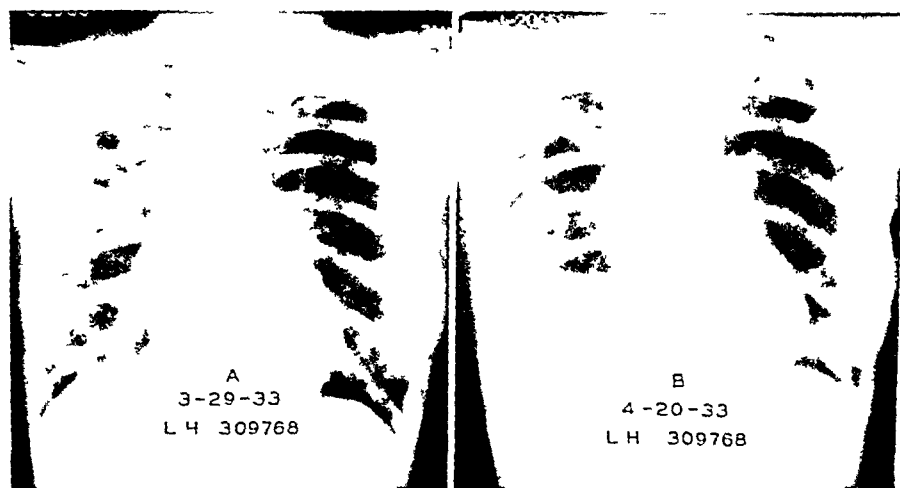


Fig. 5A

Fig. 5B

#### Case 1

Fig. 5A Infiltration of the right lung, as it appeared four days before paralysis of the right diaphragm.

Fig. 5B Atelectasis right upper lobe. Elevation right diaphragm nineteen days after crushing right phrenic nerve. The mottling seen in A in the second anterior inter-space has disappeared into the atelectatic lobe. (See also figures 1 A, B, C and D.)

finger was expectorated which gave marked but temporary relief from symptoms. Physical examination revealed palpable rhonchi, coarse rales and wheezes in the right upper chest, both anteriorly and posteriorly, with transmission to the left. At this time, the patient lost weight and had elevations of temperature to 100°F. By September 29, 1933, the atelectasis had disappeared leaving little evidence of a parenchymal lesion. A week later, bronchoscopic examination (Dr. Jones) showed the entire length of the tracheal lumen narrowed, the mucosa being scarred and multiple ulcerative lesions with considerable crusting were seen. The right main stem bronchus was narrowed

with a similar type of lesion and the bronchoscope could not be safely passed. The left main bronchus was stenosed, but admitted the bronchoscope, the mucosa being ulcerated, scarred and thickened. Relief from the distressing wheezing and decrease in cough and sputum followed this procedure.

A short time later, the patient was removed to the West in the hope that dryness and altitude (5000 feet) would be beneficial. Two years have elapsed, and only in recent months have bath-room privileges been allowed twice daily. During the past year she has been free of cough and expectoration, but still experiences, at infrequent intervals, mild wheezing.

During the hospitalization here, the treatment consisted of bed-rest and temporary paralysis of the right hemidiaphragm. Ultraviolet light irradiation and numerous cough mixtures were tried without beneficial results. When tested intracutaneously, the patient was not hypersensitive to three autogenous vaccines made from *Streptococcus viridans*, *Streptococcus haemolyticus* and *Micrococcus catarrhalis*, isolated from the sputum, nor to a vaccine of a gram-negative intracellular diplococcus isolated from the bronchoscopic aspirations from case 3. Subcutaneous tuberculin therapy was begun here and continued in the West with the addition of calcium gluconate. The expectoration of a small mucous plug and bronchoscopy were the only incidents followed by a definite change toward improvement.

5 No 323608, L. G., white, woman, 33 years of age, was admitted January, 1934, complaining only of cough and fatigue. The onset had been insidious and the duration seven months. Examination revealed an impaired percussion note over the left apex, râles in the left axilla and tubercle bacilli in the sputum. Chest X-rays, February 6, 1934 (figure 6A), showed a density fanning out from the left hilum with a small area of mottling in the periphery at the third anterior rib. The right lung was clear. Three previous X-ray examinations in the out-patient department, October and December, 1933, and January, 1934, had shown the same appearance as was seen in February, 1934 (figure 6A). A temporary paralysis of the left hemidiaphragm (Dr. Streider) was done February 17, 1934. The X-ray of March 8, 1934 (figure 6B) showed a smooth density in the right anterior second intercostal space, elevation of the left dome of the diaphragm, and an increase in shadows in the axilla at the level of the third and fourth anterior ribs, with sharply defined borders replacing the irregular mottling. One week later, a left pneumothorax was instituted, resulting in immediate collapse, partial atelectasis of both lobes and pleural effusion (figure 6C). Attention is called to the rapid appearance (figure 6B) and disappearance (figure 6C) of the density in the right second intercostal space, which had not been present in figure 6A.

Sixty to seventy per cent collapse of the left lung was maintained for four months (figure 6C), and the pleural cavity again became dry. Per-

Fig. 6A



Fig. 6B

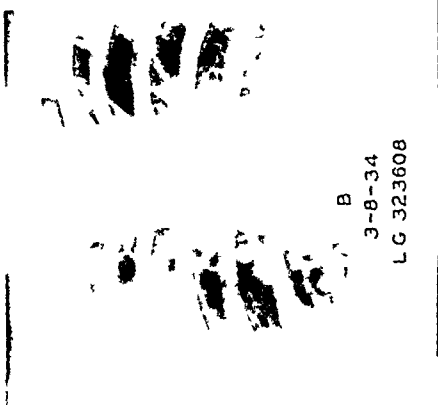


Fig. 6C

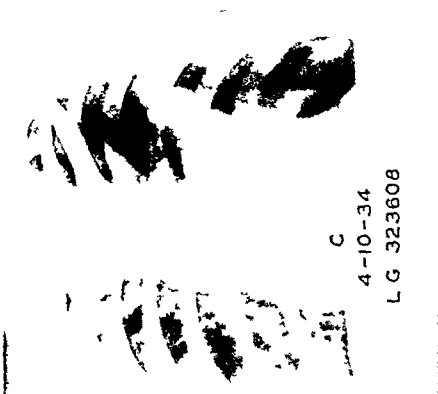


Fig. 6D

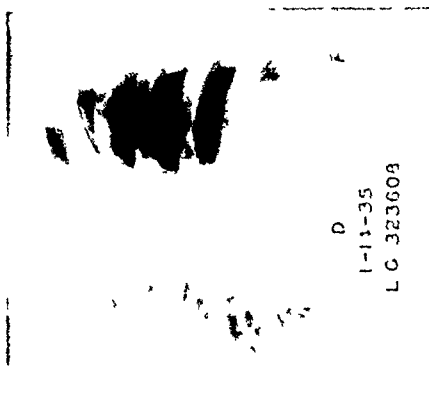


Fig. 6E

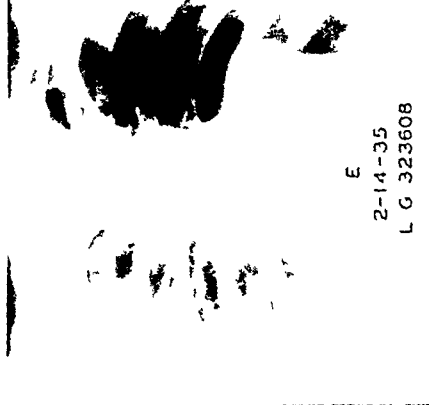
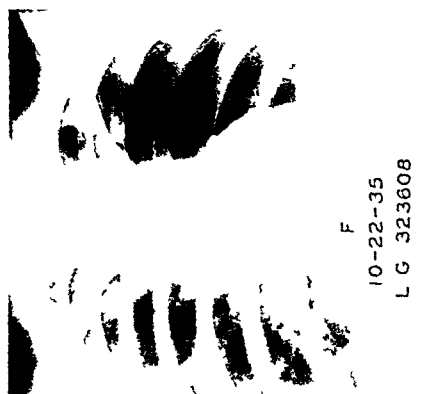


Fig. 6F



sistence of adhesions, preventing collapse of the peripheral lesion, and bacilliferous sputum led to cauterization of adhesions, August 8, 1934, by closed intrapleural pneumonolysis (Dr Alexander). The left lung was now completely collapsed (figure 6E) but still the sputum contained tubercle bacilli, and the patient was mildly cyanotic. It was at this time that questioning readily brought out the fact that the patient had experienced "wheezing" and "rattling" localized to the left upper lung during the seven months before her admission and throughout her hospitalization, unknown to the staff or referring physician. Examination at this time revealed loud expiratory parasternal rhonchi on the left, which could not be dislodged by cough, though

#### Case 5

Fig 6A. Minimal infiltration left root and in periphery at left third anterior rib. Tubercle bacilli in sputum. There is no change between shadows seen in A, from those seen in serial X rays taken from October 1933 to January, 1934, while patient was ambulatory.

Fig 6B. Development of small area of atelectasis in right second anterior interspace. This shadow was not present one month earlier in A, nor one month later in C. Elevation of partially left diaphragm, resulting in cone shaped area of atelectasis at left third anterior rib.

Fig 6C. Area of atelectasis in right lung field seen in B has disappeared and remains absent in monthly X-rays for the next eighteen months. Hydro-pneumothorax on left, collapse of both lobes with adhesion in region of original lesion. Tubercle bacilli persist in the sputum. Last refill April 9, -6-4, 250 cc, -4-1. In the left wall may be seen a haemangioma of chest wall protruding into pleural cavity.

Fig 6D. Left lower lobe is completely collapsed and has been so since intrapleural pneumonolysis in August, 1934. The left upper lobe (it has dropped to the base of the thorax—its border is seen parallel to the border of the collapsed lower lobe and midway between it and the thoracic wall) is now expanded, though the X ray two months before showed it completely collapsed, as it is again in E, taken one month later. Tubercle bacilli remain in the sputum. Last refill January 10, -8-3, 300 cc, -5-1.

Fig 6E. Both left lobes completely collapsed, one month after expansion of left upper lobe in D. Tubercle bacilli remain in sputum. Last refill January 31, -11-6, 300 cc, -7-4.

Fig 6F. Left lung has remained completely collapsed. Inspiration and expiration X rays show no change in contour of left lung. Left lung now shrunken, much smaller than when first collapsed. Tubercle bacilli in the sputum. Febrile pleural effusion on left has intervened since E. Last refill October 7, -9-3, 100 cc, -3-1.

this finding had never been reported in any of the previous two dozen routine physical examinations. A clinical diagnosis of bronchial obstruction was confirmed by bronchoscopy (Dr Furstenberg) on January 12, 1935, which showed the bronchial tree on the right to be entirely normal. On the left, however, there were ulcerations of the mucosa and exudate, but the most prominent feature was a large, red fungating tuberculoma arising from the wall of the bronchus. The lumen was entirely filled except for a narrow crescent-shaped passage. The bronchoscopy had no influence on the patient's progress, but the symptoms and signs of obstruction had disappeared spontaneously shortly before the examination.



Fig 7A

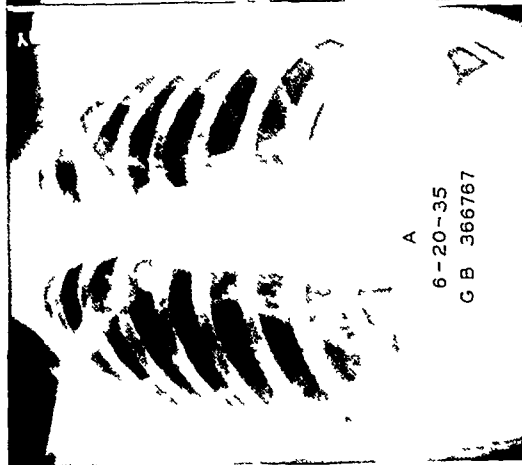


Fig 7B



Fig 7C



Fig 7D



Fig 7E



Fig 7F

A series of medium wave-length roentgen treatments were begun on January 22, 1935 and continued at weekly intervals over the upper thorax, alternating anteriorly and posteriorly. Following the seventh X-ray treatment on March 1 pleural effusion with fever developed, lasting three months. The patient lost weight and appeared more cyanotic.

Six months following the first bronchoscopy, a second examination (Dr Furstenberg) was done, and marked improvement was noted on the left. The right side remained normal. This second bronchoscopy was not done until the patient had begun a general clinical improvement which has continued. The bronchial symptoms remained absent from January, 1935, until August, when there were "wheezes" for only eight days. Temperature remained normal except for sharp rises of from 102° to 103°F on the day following pneumothorax refills or fluid aspirations. These temperature ele-

*Case 6*

Fig 7A<sup>3</sup> There is only a suggestion of abnormal shadow in the left lung just above and just below first anterior rib peripherally. Tubercle bacilli were found in the sputum at this time.

Fig 7B First out patient visit eight months after onset. Tubercle bacilli in sputum. Minimal infiltration in left apex to second anterior rib showing slight increase in the two months since A during which time patient was ambulatory. Mediastinal structures and diaphragm in normal position.

Fig 7C Eighteen days after bronchoscopy a shadow has appeared in left midlung field peripherally, where there was previously no involvement. The sudden appearance sharpness of borders suggest atelectasis, though there is no shift of mediastinal structures or diaphragm.

Fig 7D One month after C. Shift of mediastinum and heart to left and shrinkage of shadow in left midlung field.

Fig 7E Ten weeks after bronchoscopy, five weeks after beginning X-ray treatment. Elevation of left diaphragm, further shift of mediastinum to left, additional areas of atelectasis at apex and base.

Fig 7F Atelectasis of left lung practically complete three months after admission.

inations became less and less frequent. The sputum has contained tubercle bacilli almost constantly, but in fewer numbers over the past three months.

November 2, 1935 a third bronchoscopy, by the same examiner, showed again the small superficial ulcer on the lateral wall of the left bronchus, two centimeters below the crina. At a deeper level, the tuberculoma, springing from the lateral wall of this bronchus, appeared about one-third its original size.

Twenty-three months sanatorium care, four months of sixty to seventy per cent collapse, sixteen months of total collapse of the left lung (figures 6D, E & F) have failed to obliterate tubercle bacilli from the sputum.

6 No 366767, G B, white, woman, age 37 years, was admitted August 19, 1935, complaining of cough, weakness, fatigue, and a "rattle in her throat."

<sup>3</sup> X-ray furnished through courtesy of Dr E W Meredith, referring physician.

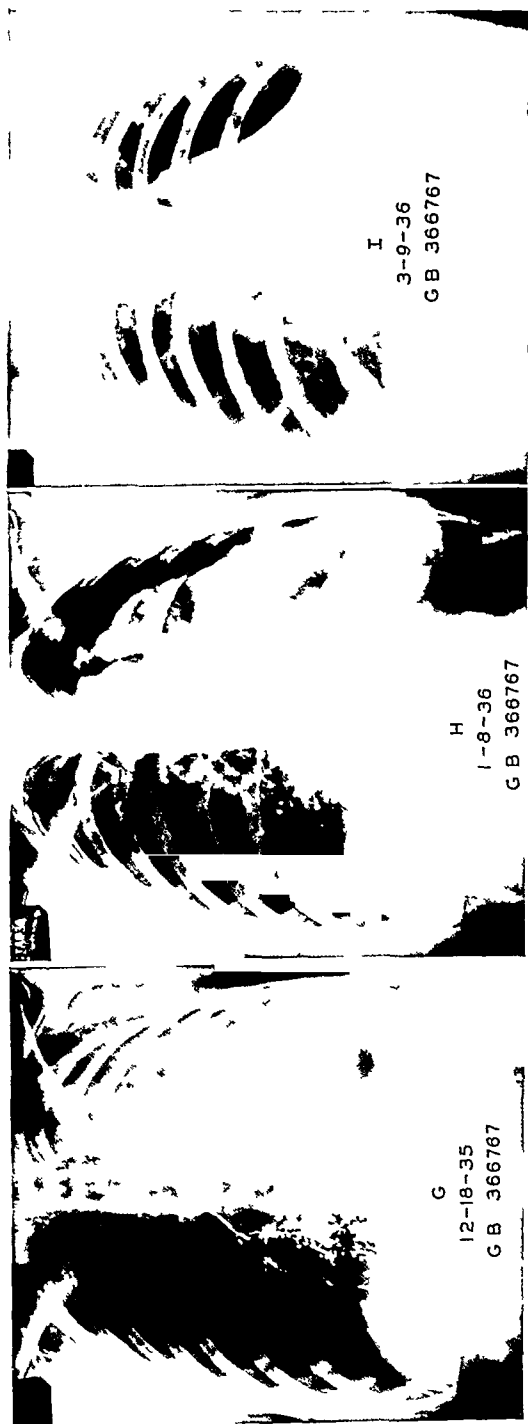


Fig 7G

Fig 7G<sup>4</sup> Lipiodol filling. The trachea is deviated to the left. The right main stem and lower lobe bronchus are patent and filled to the terminal bronchus. The left main stem is narrowed and irregular. The lipiodol penetrates but to a short distance beyond the bifurcation as compared to penetration on the right. The heart is displaced to the left and left diaphragm is elevated, but some areas of aeration remain in left lower lung field.

Fig 7H

Case 6

Fig 7H. Film taken on day of induction of pneumothorax and injection of only 300 cc of air. Atelectasis of lower lobe is more complete than in upper lobe, though the upper lobe was the original site of disease, only five months previously.

Fig 7I

Fig 7I. Atelectasis of left lung practically complete in spite of adhesions to apex and base, two months after induction of pneumothorax. Compare figures 2A, B, C and D and figures 6B, C, D and E.

<sup>4</sup> Films for figures 7G, H and I furnished through the kindness of Dr D O N Lindberg

and upper left lung " The onset of the present illness was in January, 1935, with what the patient called "flu " The symptoms were weight loss, fatigue, malaise, temperature to 102°F, heavy feeling in the anterior chest, and cough productive of small amounts of sticky sputum that were raised with difficulty During May, 1935, the patient first experienced wheezing and noticed a "rattle in her throat and upper left lung " She could feel this "rattle" or "rumble" with her hand anteriorly over the left apex, and it was audible to her husband some distance from the patient These phenomena, suggestive of bronchial obstruction, became very annoying and frightening to the patient, especially at night, and were solely responsible for her first consulting a physician A letter from the referring physician, Dr E W Meredith, Port Huron, Michigan, brings out some of the difficulties of diagnosis "At the time of her first visit to me in May the chest sounded more like an asthmatic bronchitis There were no tubercle bacilli found in the sputum at that time, and there were no definite X-ray evidences of parenchymatous involvement of the lungs (figure 7A) There was an increased density of root shadows especially on the left side Repeated examinations of the sputum, however, showed tubercle bacilli "

She rested at home until her admission here three months later, and during this period the previous symptoms continued In addition she had some shortness of breath, temperature rises to 99.4°F and occasional night sweats

Our first examination showed palpable rhonchi over the left chest, coarse râles and wheezes loudest in the left axilla and over the base of the left lung posteriorly Breath sounds were difficult to hear because of numerous asthma-like wheezes Tubercle bacilli were again demonstrated in the sputum, and chest X-ray, August 14, 1935 (figure 7B), showed a light minimal infiltration in the left apex to the second anterior rib

A clinical diagnosis of tuberculous tracheobronchitis, complicating pulmonary tuberculosis, was immediately entertained, and a few days later, August 30, 1935, the bronchoscopist (Dr Samson) found an ulcerative tuberculous tracheobronchitis and slight stenosis of the left stem bronchus at its orifice Symptomatic improvement followed, the wheezing and "rattling" gradually disappeared, the cough became less distressing, and expectoration easier

September 17, 1935, X-ray (figure 7C) showed a new shadow in the left midlung field peripherally with sharply defined borders No new physical findings were detected at this time and the temperature, pulse and respirations were normal

Sanatorium care and strict bed-rest made up the treatment till October 3, when a series of five medium wave-length roentgen ray treatments were begun, alternating over the upper anterior and posterior thorax at weekly intervals October 18, 1935, X-ray (figure 7D) showed a shift of the medi-

astinum and heart to the left and shrinkage of the shadow in the left mid-lung field. Three weeks following the beginning of X-ray treatment marked changes were noted in the physical findings of the chest. The left lung was resonant, but there was a complete absence of tactile fremitus, breath sounds and voice sounds. Approximately at the same time elevations of temperature ( $98.6^{\circ}$  to  $103^{\circ}$ ) and pulse (80 to 130) occurred and continued until the time of discharge, November 23, 1935.

November 8, 1935, she complained of pleuritic pain in the left axilla, and a transient friction rub was detected in the third intercostal space anteriorly. The left upper lung field was resonant anteriorly and posteriorly, breath sounds, tactile fremitus and voice sounds being transmitted over this area. Posteriorly, below the sixth dorsal spine, there was flatness, absent tactile fremitus, breath sounds and voice sounds. A demonstrable shift of the mediastinal structures to the left was found on percussion and palpation. X-ray (figure 7E), on the same date, showed a further shift of mediastinal structures, when compared with the previous month, and, in addition, elevation of the left dome of the diaphragm was noted for the first time. Areas of atelectasis now appeared at the apex and base of the left lung. The last X-ray (figure 7F) before discharge showed massive collapse of the left lung.

We are indebted to Dr. D. O. N. Lindberg, Decatur, Illinois, for the following data on the patient's postdischarge history and for permission to reproduce his X-rays (figures 7G, H & I).

"The sputum contained tubercle bacilli on December 2, (Gaffly V) and on December 4, 1935 (Gaffly II). The amount of air producing the pneumothorax seen on films dated January 8, 1936 (figure 7H) was 300 cubic centimeters. The first refill was given one day later and 450 cubic centimeters resulted in very little additional compression. The next (concentration sputum) examination was made on February 6, 1936, or less than thirty days from time of institution of induced pneumothorax, and no tubercle bacilli were found. She has gained four and one-half pounds in weight. She has been free (of fever) for two months. All constitutional symptoms are absent."

#### DISCUSSION

*Extent of pulmonary lesion.* One of the most striking features of this series of cases is the small extent of the pulmonary focus of tuberculosis when the patient first came under observation. The extent of the lesion seemed to have no parallelism with the severity of the symptoms or the downward course of the illness. Of the four patients who died of the complication of ulcerative tuberculous tracheobronchitis, two were classified as minimal when first seen and two were in the moderately

advanced group    Minimal and moderately advanced pulmonary tuberculosis is usually amenable to treatment of the simplest sort, but these patients progressed to death in spite of, or because of, every known method of giving rest to the body and to the diseased lung    Only one of our nine patients with ulcerative tuberculous tracheobronchitis was classified as far advanced on admission    Furthermore, only one of our cases had tuberculous complications outside of the respiratory tract, so that the failure of treatment cannot be ascribed to a general breakdown of bodily resistance to the tubercle bacillus    This fact is further borne out by the studies of autopsy material (Bugher, Littig and Culp (16))

*Tubercle bacilli in the sputum*    It is not remarkable that all cases had tubercle bacilli in the sputum, but tubercle bacilli appeared and persisted in these cases under circumstances which we considered unusual    In case 6 tubercle bacilli were found in the sputum before an unequivocal roentgenological diagnosis could be made    At the time of the finding of the tubercle bacilli, there was no other point on which to base a diagnosis or even to form a presumption of tuberculosis    In other cases of minimal pulmonary tuberculosis, the sputum contained tubercle bacilli long beyond the usual period of treatment given to patients with minimal pulmonary tuberculosis    This fact led to the inauguration of a long series of collapse measures in case 5    The most serious disappointment has been the finding that collapse, even total collapse of the involved lung, has not rendered the sputum free of tubercle bacilli (cases 2 and 5)    The conclusion must be drawn, and the bronchoscopic studies (Samson (15)) and the pathological studies (Bugher, Littig and Culp (16)) support the conclusion, that the tracheal and bronchial ulcers are a source of tubercle bacilli in the sputum    The bearing of this point on the indications for bronchoscopy and the indications for collapse therapy are dealt with in a subsequent section    The presence of tubercle bacilli in the sputum of patients whose pulmonary lesions, as revealed by the X-ray, do not fully explain the presence of tubercle bacilli in the sputum, should naturally arouse the suspicion that tracheal or bronchial ulcers exist

*The complication as the cause of the chief complaint*    In three of our cases the wheezes, rattles and other symptoms of partial bronchial obstruction formed the chief complaints and the first symptoms of tuberculosis (cases 2, 4 & 6)    In two the diagnosis of asthma had been made prior to admission    In all but one the symptoms of the complication

as contrasted to the usual symptoms of pulmonary tuberculosis remained the chief and dominating complaint throughout the patient's illness. In that one exception (case 5) the symptoms were so slight that the patient had been under treatment for a year before the complication was suspected.

*Atelectasis<sup>5</sup> as a feature of the complication* The intriguing behavior of the right upper lobe in case 1, which was now atelectatic and again inflated in serial X-rays (figures 1A to D), first led us to investigate a bronchial cause for this phenomenon. We had expected to find a broncholith partially or completely occluding the right upper lobe bronchus. Instead the bronchoscopist found a large ulcer of the bronchus surrounded by oedematous mucous membrane. A biopsy confirmed the impression that the ulcer was tuberculous, though this was a needless and probably harmful addition in the presence of tubercle bacilli freely demonstrable in the sputum. That the right upper lobe had been intermittently atelectatic there could be no doubt, for as Dr. Henry Field, Jr. pointed out, whenever the homogeneous density appeared, the mottling in the first anterior interspace disappeared. The mottling in the first interspace could have disappeared nowhere else except into the atelectatic upper lobe, for whenever the shadow of atelectasis disappeared the characteristic mottling reappeared in the first interspace. This phenomenon appeared on many serial X-rays not reproduced in this report. The fact that there was no displacement of the trachea in this case, we believe, is evidence that atelectasis of a lobe may be compensated wholly by emphysema of other parts of the lung, and that displacement of the trachea should not be demanded as a criterion of atelectasis. When the position of the trachea is fixed by surrounding inflammation, the possibility of atelectasis is not removed, at autopsy the trachea in this case was so fixed. There was atelectasis then, and there was ulceration and oedema of the bronchus, and there were the symptoms associated with bronchial obstruction. The picture could be reconstructed only by assuming that the oedema was not constant in amount, and that when the oedema became intense the wall of the bronchus would be so thickened and in consequence the lumen so narrowed,

<sup>5</sup> The term *atelectasis* has been used here to describe the sudden development of airlessness in the presence of cause for bronchial occlusion. We believe that initially the condition will be pure atelectasis. It will probably not remain so in a lung with known tuberculous foci which is supplied by infected bronchi with drainage blocked. Autopsies obtained months after the onset will not yield evidence of the pure atelectasis that originally obtained.

that partial obstruction obtained. If, in addition, thick, tenacious sputum entered the narrowed lumen, the obstruction would become complete and varying degrees of atelectasis would be found in the next serial X-ray depending upon the time interval between the occurrence of the obstruction and the making of the X-ray exposure. Subsidence of the oedema or dislodging of the mucous contained in the lumen would allow inflation of the lobe. This seemed a likely explanation of the events observed and the hypothesis has served to interpret many changes seen subsequently in this and other patients.

If this could happen so readily in a major bronchus, it seemed all the more likely to happen in smaller bronchi. If it should happen in a smaller bronchus, there is the possibility that the collateral respiration, which Van Allen and Soo (17) found in healthy animals, would maintain aeration and prevent atelectasis in the area supplied by that bronchus. In tuberculosis of the bronchi there is every reason to suppose, however, that tuberculous disease of the parenchyma and its exudates frequently seal these channels to collateral respiration and so allow the possibility of localized or lobular atelectasis. Given tuberculous disease of the parenchyma and tuberculous processes in the walls of the bronchi capable of producing occlusion, we may expect to find areas of atelectasis of any size from very small anatomical subdivisions of a lobe up to that of a whole lobe or a whole lung. Such has been our interpretation of many of the shadows that we have seen in the X-rays of patients with ulcerative tuberculous tracheobronchitis.

In case 5 (figures 6A to C), a small density appears in the second right anterior intercostal space which was not present the month before and which leaves no remnant the month after its appearance. This is a reproduction on a small scale of the appearance and disappearance of lobar atelectasis in case 1. The suddenness of the appearance and of the disappearance is, we believe, good argument that it was atelectasis rather than infiltration.

In case 2 (figures 2A & B), we saw the development of atelectasis of the lower lobe, and in this case the diagnosis of atelectasis is supported by the retraction of the heart and the elevation of the diaphragm.

In case 6, we saw the development of atelectasis from the patchy, lobular stage (figure 7C) through the aggregation of other lobular areas to involve almost the entire left lung with only a few areas of aeration remaining (figures 7C to G). The diagnosis of atelectasis in the later X-rays is again supported by retraction of the trachea and mediastinal



structures and by the elevation of the diaphragm. We believe the earlier shadows were also atelectatic in origin because of their sudden appearance (figures 7B & C). Pulmonary tuberculosis, as usually seen in serial X-rays, does not behave in this fashion. The lesion did not extend from the initial lesion, as is usual, it did not appear in one of the usual sites for a bronchogenic dissemination, it had much more sharply defined borders than is seen in a tuberculous lesion of such recent origin, and it had a homogenous appearance. The whole left lung became dense with shadow in an extremely short time (there are only three months between B and F of figure 7), no cavities appeared, and it could not have been caseous pneumonia for retraction appeared early and increased as the shadows extended.

The lipiodol filling in figure 7G shows nicely how the swelling and thickening of the left bronchial mucosa has narrowed the lumen. The bronchi plugged with lipiodol are close to the bifurcation and normally have a much larger lumen than is shown in this film. The lipiodol in this instance demonstrates the possibility of thick sputum producing a similar plugging of such narrowed bronchi. Compare the wide lumen and the basal filling of the bronchi in the right lung.

*Factors conducive to atelectasis* The pathological conditions present and their anatomical distribution in tuberculous ulcerations of the bronchi tend naturally toward the development of atelectasis. Physiological considerations suggest that many of the routine measures adopted to give rest to the body and the lungs in the treatment of pulmonary tuberculosis would favor the development of atelectasis in such cases. Anything which would tend to shorten the bronchi, and so relatively increase the thickness of the swollen mucous membrane, would narrow the lumen and enhance the likelihood of obstruction and consequent atelectasis. The length of the bronchi is decreased in the midposition of respiration by placing the patient at bed rest and discouraging deep breathing and other respiratory effort, the bronchi are further shortened by any and all methods of collapse of the lung. A third possible factor in our treatment of these cases that has contributed toward the development of atelectasis has been the use of X-ray therapy. If X-ray therapy produces some immediate swelling of the inflamed mucosa, then the additional thickness of the bronchial wall might be sufficient to cause bronchial obstruction and therefore atelectasis. A fourth possibility in our cases is that the trauma of the bronchoscopic examination may have produced the necessary swelling to occlude the bronchus. The

bearing of each of these four factors on the cases reported is discussed separately in the succeeding paragraphs

*Bed-rest and hypoventilation* Surgical experience with postoperative atelectasis indicates that shallow breathing is a factor in the production of atelectasis. The type of rest given routinely to patients first admitted to sanatoria for the tuberculous is designed to reduce the respiratory effort to a minimum. If a patient with a swollen bronchial mucosa is placed on such a regimen of enforced rest, and if beyond the point of the swelling in the bronchus there is a source for secretions, it is not surprising that the concurrence of these factors should be attended by the first production of atelectasis.

Case 2 had complained of rattles in the chest for at least two years before sanatorium treatment was instituted. In that period of two years, X-rays taken at the beginning and the end of the period showed little change in a minimal basal lesion. After four months of bed-rest, with no other treatment and before bronchoscopy was done, there was massive atelectasis of the left base.

Case 5 had experienced wheezing for five months before admission to the hospital, and had been observed by serial X-rays for three months as an out-patient without the development of atelectasis and with no change in the parenchymal lesion. Within a month of the inauguration of strict bed-rest in the hospital, transient atelectasis developed in the right lung which received no collapse therapy and before bronchoscopic examination was done.

The effect of bed-rest in case 6 is less definite as X-ray evidence of atelectasis did not appear until after the bronchoscopy, but it can be said that the course of the disease was worse after the institution of treatment than it had been before admission to the hospital. She had had symptoms of the complication for six months before the first X-ray examination (figure 7A) which showed no evidence of atelectasis and little evidence of any disease. At the time of admission, the duration of the disease had been eight months, and the X-ray (figure 7B) still gave no evidence of atelectasis. Within three months of the institution of treatment, atelectasis of the left lung was nearly complete (figure 7F).

*Production of atelectasis by collapse therapy* Collapse of the lung by any method results in some relaxation of the lung and some shortening of the bronchi. This is obvious in lungs collapsed by pneumothorax, thoracoplasty and paraffin pneumonolysis when the X-rays actually show the lessened distance between the root and the periphery of the

lung in at least one plane. In paralysis of the diaphragm, it is obvious only in basal lesions when the distance between the lesion and the root of the lung can be shown to be shortened at least in inspiration. We believe, however, that a similar effect can be demonstrated in many upper lobe lesions, when the shortening of the distance between root and periphery is affected by an elevation of the root. There is the additional factor of distortion of the bronchi by reason of a change in the direction of their axes following many forms of collapse.<sup>6</sup>

Shortening of the bronchi by collapse naturally does not affect the diameter of the cartilagenous rings and the outer wall of the bronchi. In ulceration of the mucous membrane, there is, however, an associated swelling and oedema as is shown in the lipiodol filling in case 6 (figure 7G) made before the institution of collapse. When the bronchi are shortened by collapse, this swollen bronchial lining is thickened by the gathering up of its length into a shorter space. The bronchial lumen may be sufficiently narrowed by this mechanical action alone to produce obstruction and atelectasis, without the probable additional factor of thick secretions plugging the narrowed lumen. Four of the six cases chosen for this report illustrate this effect of collapse therapy in the presence of ulcerative tuberculous tracheobronchitis.

*Paralysis of the diaphragm.* The symptoms of partial bronchial obstruction had been present in case 4 for a year before admission, yet there was no evidence of atelectasis in the admission X-ray (figure 5A). Nineteen days after paralysis of the right diaphragm by crushing the nerve, atelectasis of the right upper lobe is present in the X-ray (figure 5B). This response to phrenic paralysis is in accord with our hypothesis and it has appeared to us as so typical that its occurrence should suggest the possibility of tuberculous tracheobronchitis.<sup>7</sup>

There is some indication that a similar effect followed diaphragmatic paralysis in case 5. The changes in the shadows in the left lung in figure 6 between A and B suggest that atelectasis has taken place fol-

<sup>6</sup> When Dr. T. T. Wang of the Peiping Union Medical College was visiting this clinic, he was shown the X-rays on case 4. He said that he and Dr. C. M. Van Allen had entertained this hypothesis and had construed it as a contraindication to collapse therapy when bronchial disease was present.

<sup>7</sup> This typical response to phrenic paralysis was noted in the serial X-rays sent to Dr. Kirby S. Howlett, Jr., then a member of the staff of this hospital. In writing his report of the X-rays, Dr. Howlett mentioned our suggestion that the X-rays gave some evidence that bronchial occlusion had followed the phrenic paralysis. Dr. Howlett later heard from the referring physician that bronchoscopy had confirmed the diagnosis of ulcerative tuberculous tracheobronchitis. This diagnosis had been hazarded on the evidence in the X-rays alone.

lowing the elevation of the diaphragm In B, the shadow has more sharply defined edges and it is triangular in shape

Even though the diaphragm is not elevated enough to effect changes in the direction of the bronchus or changes in the bronchial length, the effect of the paralysis on the depth of respiration might be sufficient to allow occlusion of the thickened bronchial walls

*Atelectasis in pneumothorax* The X-ray picture of tuberculous areas of the lung collapsed by pneumothorax is often indistinguishable from areas of atelectasis The collapsed areas probably contain both areas of atelectasis and areas of tuberculous pneumonia which form one homogeneous shadow These homogeneous densities, however, always appear in the lobe and usually in that part of the lobe which showed the tuberculous involvement before the pneumothorax was induced This is a common picture in selective collapse by pneumothorax The selective collapse may be confined to one lobe or to only a part of a lobe, the parts of the lung which were free of disease remain aerated as long as the intrapleural pressures are kept subatmospheric The collapse of the diseased areas seems to be due to retractile forces inherent in the diseased tissue, it is not due to bronchial obstruction since drainage from the area remains free and cavities empty themselves of their secretions which are expectorated

We have never seen the picture just described of selective pneumothorax in patients with ulcerative tuberculous tracheobronchitis Instead of selective collapse of the involved area of the lung only, we have witnessed rather sudden and total collapse of a whole lobe or of a whole lung even though the lesion before pneumothorax occupied only a very small part of one lobe The suddenness of the collapse has been as conspicuous as the totality of the collapse In the absence of bronchial occlusion, pneumothorax allows a rather slow progressive collapse of the involved areas When pneumothorax shortens the bronchi and allows the thickened walls to obstruct the bronchus, a very marked degree of collapse is found at the very next fluoroscopic or roentgenographic examination

In case 2 (figure 2) the original disease and the atelectasis existing before the pneumothorax was induced were confined to the left base, while the left upper lobe remained clear in every X-ray taken over a period of two and a half years The first X-ray, taken only two days after induction of the pneumothorax, showed an airless left upper lobe which had never before been involved

In case 5 the original lesion was confined to a very small area in the left lower lobe (figures 6A & B). In the absence of bronchial occlusion, one would expect pneumothorax to permit selective collapse of this small area, but one would expect the remainder of the lower lobe to remain aerated while negative intrapleural pressures prevailed. Instead, both lobes became almost completely atelectatic (figure 6C). After the adhesion to the lower lobe was severed by cautery, this lobe never again became aerated, though the intrapleural pressures were well subatmospheric. The upper lobe, which had been free of disease, behaved curiously, for, in serial monthly X-rays, it would be atelectatic on one occasion and aerated on the next. The intermittent atelectasis of the left upper lobe repeated itself through a long series of serial X-rays, two of which are reproduced (figures 6D & E). The behavior of this upper lobe resembled that of the right upper lobe in case 1 (figures 1A, B, C & D). In addition to the factors responsible for the inconstancy of the atelectasis in case 1, there was, in this case (case 5), the variations in intrapleural pressures and consequent variation in length of the bronchi. The more negative the intrapleural pressures, the greater the pull on the lung, and this pull stretches the contained bronchi and so thins the mucosal wall to the point that air might enter the lobe. When a refill of air would reduce the intrapleural pressures below this critical level, the bronchial walls would come in contact and produce occlusion.<sup>8</sup> The nature of the collapse in case 5 was one of the elements which led to the clinical diagnosis of tuberculous tracheobronchitis and bronchoscopic examination.

The atelectasis was practically complete in case 6 (figure 7) before pneumothorax was induced, but it is interesting that the response of this lung to pneumothorax was predicted before the attempt was made.

<sup>8</sup> A patient, not included in this series because of her inability to cooperate during an attempted bronchoscopy, had all the signs, symptoms, and X-ray characteristics of obstructive atelectasis of the right upper lobe due to tuberculous bronchitis. Cavities, seen in the right upper lobe in X-rays previous to admission, had disappeared in the admission X-rays. The right upper lobe was represented only by a narrow rectangular density extending from the root upward along the shadow of the spinal column. Pneumothorax on the right failed to influence the symptoms or the sputum. After a year, reexpansion of the pneumothorax resulted in an exacerbation of all the symptoms. The right upper lobe reexpanded under high negative pressures, and the cavities reappeared. When pneumothorax refills were resumed after a two months lapse, the right upper lobe again became atelectatic. The patient was improved symptomatically, but tubercle bacilli remained in the sputum.

Case 3 of this series showed a similar harmful reaction to reexpansion of a lung collapsed by pneumothorax for three years.

*Medium-length roentgen-ray therapy* We have personally observed two patients with tuberculous ulcers of the trachea and bronchi that were subjected to medium wave-length roentgen-ray treatment<sup>9</sup> In one of these (case 6, figure 7) there is the suggestion that the treatment contributed to the rapid development of atelectasis Some atelectasis had developed after the bronchoscopy and before the roentgen-ray treatments were begun (figure 7C) Within six weeks of the beginning of the treatment, atelectasis of the entire lung was practically complete (figure 7F), and the treatments had to be discontinued because of the symptomatic response The evidence of the swollen mucosa is amply demonstrated in the lipiodol filling (figure 7G) It is the opinion of the bronchoscopist (Dr Samson) that the swelling portrayed in this X-ray is greater than that seen by him through the bronchoscope Whether or not this is the case, it is reasonable to suppose that the immediate response of an inflamed mucosa to X-ray treatment would be some additional swelling How long the reaction might last cannot be said, but it is certain in this case that at the time of the lipiodol filling, five weeks after the end of the treatment, there was still swelling of the mucosa If the original swelling is followed by a shrinkage attributable to the X-ray treatment, then that shrinkage did not take place within the five weeks covered by this observation

What other effects, beneficial or harmful, there may be from X-ray treatment in this condition cannot be said In case 5 the X-ray treatment was resorted to because of the failure of all other forms of treatment in this condition and because there was in this case a definite tuberculoma of the bronchus It was assumed that tuberculoma, being of a somewhat similar pathological structure to a tuberculous lymph node, might respond as tuberculous cervical lymph nodes do to this form of treatment The tuberculoma was observed bronchoscopically before the treatment was begun and at three and eight months after the treatment was ended The same observer reported that to the best of his visual memory there was reduction in the size of the tuberculoma on each succeeding examination On the final examination, it was about one-third of its original size An ulcer reported in the same case, however, was not reported as in any way changed following the X-ray treatments The treatments in this case were terminated short

<sup>9</sup> The dosage of each treatment was 350 r The roentgen therapy and roentgenological diagnostic studies were conducted by the Department of Roentgenology of the University of Michigan Hospital under the late Dr Preston M Hickey and his successor Dr Fred J Hodges

of the intended dosage because of the development of a febrile pleural effusion which ran a three months course, and which differed in no way from similar courses in other patients undergoing therapeutic pneumothorax. The symptoms of bronchial obstruction had disappeared before the treatments were begun and returned for a period of only eight days, five months after the X-ray treatments.

The evidence, therefore, of beneficial effect of this form of treatment is rather dubious, and it seems probable that from one experience the treatment should not be employed in those cases showing a highly inflamed and swollen mucosa unless there is found reason to believe that obstructive atelectasis is beneficial in these cases. If that is found to be the case, then X-ray therapy is possibly a means toward that end.

*Bronchoscopy* In this report, the possible harm of bronchoscopic examination is purposely emphasized. It is true that most of the instances of possible harm from this examination occurred during our earlier experience with these cases, and in cases in which needless biopsies were taken, nevertheless, they should serve as a warning, particularly to those bronchoscopists who may be asked to examine such patients for the first time.

Even though the examination is done as gently as possible, the mere passage of a stiff metal tube over inflamed mucosa may produce enough additional swelling to occlude a bronchus that was previously patent. In the examination of case 6, the bronchoscopist did not attempt to pass the bronchoscope beyond the narrowing in the left bronchus. It cannot be proved nor disproved that the sudden appearance of an area of atelectasis in the X-ray (figure 7C), taken eighteen days after the examination, was due to the trauma of the bronchoscopy.

Whether or not the bronchoscopy is a factor in the production of atelectasis in our cases, the examination has been followed by definitely harmful reactions in two and by definite benefit in four. The bad results occurred under two circumstances. In case 1, the bronchoscope was passed over a trachea that was already narrowed by oedema and swelling, and this was followed by symptoms of suffocation. In case 2, attempts to remove the obstructing crusts from an ulcer resulted in bleeding and further crusting with greater obstruction. On the other hand, temporary relief of symptoms has followed both a simple diagnostic examination and the removal of obstructing material such as inspissated mucous plugs.

Because of the possibility of harm, we are not recommending bronchos-

copy except in those cases where the diagnosis of ulcerations would affect the treatment to be used, and in those cases in which impending suffocation demands a bronchoscopic attempt at relief. The indication first mentioned is justified because the diagnosis of tracheal or bronchial ulceration may prevent the inauguration of a long, useless and perhaps harmful program of collapse therapy. This indication is limited to that group of patients in whom the indications for collapse are to be found primarily in the persistence of tubercle bacilli in the sputum, but in whom the anatomicopathological indications for collapse therapy are not present in the X-rays. In this group, the source of the tubercle bacilli may be the tracheobronchial ulcers rather than the parenchymal lesion. Inasmuch as collapse of the lung will not affect the bronchial lesions nor the bacilliferous sputum arising from these lesions, diagnostic bronchoscopy should be employed to rule out this source of the tubercle bacilli before collapse therapy is undertaken. Cases 2 and 5 illustrate the futility of collapse in this group. In these two cases bronchoscopic diagnosis of ulcerative tracheobronchitis was not made until after a long series of fruitless collapse measures had been employed. In case 6 bronchoscopy was employed for the specific purpose of determining this point before deciding on collapse therapy.

The two indications for bronchoscopy just given are the only two that we have found to be of any benefit to the patient. It is undoubtedly true that we have seen a very limited sample of patients with ulcerative tracheobronchitis since we have tried to adhere to these indications. The very limitation of the indications for bronchoscopy to this narrow field may have allowed us to see only those patients with the poorest prognosis. It is quite possible that, with a wider application of the bronchoscope for diagnosis, we may have to revise our concept of the complication, its prognostic import and its effect on treatment. By definition, the ulcerative form of tracheobronchitis can be diagnosed only by the bronchoscope, and yet the examination of itself may have played a part in the results we have obtained. It may be that we have been "pulling our plant up by the roots to see how it grows." With our present procedure in examination, there is no way of learning the wholly natural evolution of this form of tuberculosis.

*The effect of atelectasis on symptoms.* In case 1 we had an opportunity to study the changes in symptoms in a patient with recurrent atelectasis of the right upper lobe undisturbed by collapse therapy, bronchoscopy or any treatment other than bed-rest for a period of nineteen months.



Both the symptoms of bronchial obstruction and the atelectasis were intermittent and recurrent, but we could discover no definite time relation between the two events. No fluoroscopic or roentgenographic examination was made during any of the periods of acute respiratory distress, but the atelectasis was both present and absent during periods of comparative comfort. Though the patient died of suffocation, there was no atelectasis in the right upper lobe at autopsy.

The most prominent and constant symptom of the complication is wheezing which is produced by the passage of air through a narrowed or partially obstructed bronchus. If the obstruction becomes complete and no air passes through the bronchus, and if there are no other areas of narrowing of the airway, the wheezing can no longer take place. The atelectasis is obstructive in nature, and no air passes in or out of the bronchus to the atelectatic lobe or lobes. This fact may explain the results that McConkey and Greenberg (4) reported as due to pneumothorax. If, by giving pneumothorax, these authors shortened the bronchi and thus thickened the mucosa to the point of making the obstruction complete, the collapsed lung would cease to inspire, and the symptom of the obstruction disappear though the obstruction would remain. This may also explain the absence of symptoms in our case 6 after the induction of pneumothorax. These facts would also explain the persistence of wheezing in our cases 2, 3, 4 and 5 after collapse therapy, for, if there were other areas of partial obstruction anywhere in the bronchial tree, or, if the obstruction were not made complete by the degree of collapse obtained, the symptoms of partial obstruction would persist.

*The effect of atelectasis on the bronchial and pulmonary lesions.* We have but two autopsy observations on the end-result of obstructive atelectasis produced by ulcerative tuberculous tracheobronchitis. In case 1, where no collapse therapy was used, the atelectasis was intermittent for nineteen months, but was absent in all X-ray observations for the nine months preceding death. The X-ray observations pointed to a slow but definite clearing of the involved lobe. At autopsy this lobe contained only apparently healed lesions.

In case 2, total collapse of the lung had been maintained for thirty-eight months before death. The pulmonary parenchyma was practically destroyed, the bronchi were ulcerated and markedly dilated (figure 3). The bronchi were filled with an inspissated gelatinous material that protruded above the cut surface. It is probable that this material

contributed to the suffocative death. Air could not be inspired into the lung after the obstructive atelectasis occurred, so that the accumulation of this material could not be coughed out. As it accumulated, it exuded into the bifurcation and obstructed the airway to the good lung. This mechanism could account for the attacks of dyspnoea and wheezing that had occurred with no relation to the injection or withdrawal of air from the pneumothorax cavity. It seems probable to us that the collapse of this lung had contributed to the fatal result by making the bronchial obstruction more complete and permanent, and by interfering with the effectiveness of cough.

Our other observations on obstructive atelectasis are derived only from the X-rays and the clinical course. In case 2, whose autopsy is reported in the preceding paragraph, the X-rays showed a progressive shrinkage of the collapsed and atelectatic lung (figures 2C & D). In case 5 the X-rays show an even more marked shrinkage of the left lung (figures 6E & F). It can only be surmised that the lung in case 5 was undergoing the same changes that were found in the lung of case 2. In case 2, attempts to reexpand the lung before death met with failure. In case 5, extremely high negative intrapleural pressures brought about no change in the contour of the atelectatic lung. In this case the greater part of the lung appeared healthy before obstructive atelectasis was produced by collapse. Partial reexpansion should occur under the negative pressures used, unless some complicating factor is preventing the reexpansion. This factor, of course, might be thickening of the visceral pleura following the pleural effusion. There are good reasons, however, for believing that it is not thickened visceral pleura that is maintaining the lung in this contracted state. For at least six months after the pleural effusion was controlled, the left upper lobe was found capable of reexpansion. When reexpanded the visceral pleura did not appear thickened (figure 6D). It is reasonable to assume, therefore, that reexpansion is prevented by obstructive atelectasis, and this in a lobe that appeared free of disease in serial X-rays covering a period of sixteen months before the atelectasis became permanent.

In assessing the effect of atelectasis on the pulmonary and bronchial lesions, it must be remembered that the atelectasis, which follows collapse in this complication, is obstructive, that, in contrast to the collapse produced artificially in treating pulmonary tuberculosis in the absence of this complication, there is no drainage from the infected areas. We have reported observations which seem to point to the fact

that obstructive atelectasis in these cases is harmful rather than beneficial. We do not believe these observations are conclusive on this point. Until it is known whether or not obstructive atelectasis is desirable, we cannot know how to advise patients with this complication—ulcerative tuberculous tracheobronchitis. It has been suggested that many of the procedures used now to treat pulmonary tuberculosis, including collapse therapy, are conducive to obstructive atelectasis.

#### SUMMARY

The six cases reported represent the significant peculiarities associated with ulcerative tuberculous tracheobronchitis when it complicates pulmonary tuberculosis. While they have been varied, the following symptoms and signs have been common to the group and have served in the recognition of cases with this complication.

*Symptoms* (1) Shortness of breath may occur early, before the appearance of other symptoms, and may be brought on by slight exertion, later, acute attacks of dyspnoea, or even orthopnoea, occur and are often associated with asthma-like wheezing.

(2) Wheezing, rattle or palpable rhonchi may be inspiratory, expiratory or both, and are not readily dislodged by cough. They may be generalized over both lung fields or subjectively localized beneath the sternum, to one side of the chest, or even to a small area over a single lobe.

(3) A sense of oppression in the chest is common and is frequently localized to the area of the rhonchi.

(4) Paroxysms of violent coughing are characteristic. Dramatic relief has followed the expectoration of a well-formed bronchial plug, but this is not the rule as the sputum is usually glary and tenacious, and its expectoration after great effort, usually brings only partial relief.

(5) Cyanosis is often present and is usually in excess of that to be expected from the extent of the pulmonary lesion. Cyanosis may be transient during violent paroxysms of coughing, wheezing and dyspnoea, or may be constantly present to a mild degree.

(6) Symptoms frequently are brought on or aggravated by change of posture.

(7) The injection or removal of air in pneumothorax patients with this complication bears no constant relationship to the aggravation or relief of symptoms.

*Physical Signs* The physical examination, when done carefully and repeatedly, is significant. We wish to emphasize, as do McConkey and Greenberg, the importance of localized rhonchi. These rhonchi persist following cough and are often palpable directly over the affected bronchus. Coarse râles, rattles and groans often obscure the underlying breath sounds. During unilateral complete obstruction, the breath sounds are absent over the affected lung. Signs of shift of the mediastinum toward the affected side and of elevation of the diaphragm on that side are confirmatory, but their absence is frequent. The physical examination alone will not suffice for a diagnosis, but it may often give the first suggestion and is usually confirmatory. Variability in the findings depend on the location, completeness and constancy of the obstruction. Therefore, repeated physical examinations may be necessary to detect any evidence of the complication and are necessary to follow the frequent changes.

*Diagnosis* Any of the signs and symptoms enumerated in the two preceding sections suggest the diagnosis of ulcerative tuberculous tracheobronchitis.

Serial chest X-rays often suggest the diagnosis by the sudden appearance of transient shadows of lobar or lobular atelectasis, and by the suddenness and totality of the collapse of healthy portions of the lung following paralysis of the diaphragm or induction of pneumothorax.

Lipiodol instillation may outline irregularities of the tracheal or bronchial lumen, but the interpretation of these irregularities is uncertain, and their absence does not exclude ulcerations on surfaces not outlined in the silhouette.

The persistence of tubercle bacilli in the sputum in noncavernous minimal pulmonary tuberculosis adequately treated, the presence of tubercle bacilli in the sputum in patients with indefinite X-ray evidence of tuberculosis, and the persistence of tubercle bacilli in the sputum in patients with total collapse of the pulmonary lesion, all suggest that the tubercle bacilli arise from mucosal ulcers.

Visualization of ulcers of the mucosa by bronchoscopy is the only certain method of making the diagnosis. In patients with positive sputum, confirmation of the diagnosis by biopsy is unnecessary and dangerous.

*Treatment* Antispasmodics, elimination of common protein allergens, tuberculin therapy, ultraviolet light, croup tents and various cough

mixtures have failed to relieve the symptoms or in any way to alter the course of the disease

Local applications to the ulcers have not been attempted for three reasons <sup>10</sup> (1) We have observed that individual ulcers without treatment directed toward the lesion have healed in patients who eventually died as a direct result of mucosal lesions in other parts of the tracheobronchial tree (2) As brought out in the pathological studies of Bugher, Littig and Culp, the lesions are seldom single, but tend to diffuse involvement of the trachea and bronchi, though the bronchial lesion may be unilateral (3) The lesions are usually associated with oedema which may be intensified by trauma of the bronchoscopic application

Medium wave-length roentgen treatments have been administered in two cases with ulcerations. In one, it was followed by reduction in size of a tuberculoma, but by no other change. In another, the treatments were interrupted because of the development of fever and the further production of atelectasis (see Discussion)

Bugher, Littig and Culp present evidence that the bronchial and tracheal ulcerations are secondary disseminations from pulmonary foci. It would therefore be expected that control of the pulmonary lesion would be a prerequisite to control of the tracheal and bronchial lesions. It would also be expected that adequate collapse of the pulmonary focus would be beneficial to secondary infection in the tracheobronchial mucosa, just as collapse of the source of sputum is beneficial to laryngeal tuberculosis. These expectations, however, have not been borne out by our experience. Cases 2 and 5 have been cited to show complete collapse of the diseased lung without influencing the symptoms or fatal outcome in case 2, or without influencing the ulcer or positive sputum in case 5. *Bilateral pneumothorax* in case 3 failed to prevent the onset of symptoms and failed to influence the behavior of the ulcerative lesions which resulted in a suffocative death. Phrenic paralysis in case 4, similarly, failed to affect the symptoms and failed to affect the positive sputum. We have employed some form of collapse therapy in six patients with ulcerative lesions and have observed no benefit to any of the six <sup>11</sup>

The complication is occasionally seen in patients with large unilateral

<sup>10</sup> Dilatation of cicatricial stenoses is not considered in this report on the ulcerative form of the complication

<sup>11</sup> Case 6 has recently been treated by pneumothorax in another institution and is not included in this number. The immediate results are reported as favorable

cavities, in whom the indications for some form of collapse are imperative. In these, the choice is between two evils as brought out by Eloesser, with whom we agree that the collapse should be risked in spite of the fact that collapse does not yield the results in these cases that it does in cases without the bronchial complication. The fact must be faced that death from the bronchial complication is a possibility with or without collapse, but that death from the pulmonary tuberculosis is even more certain without collapse. The cavernous source of the tubercle bacilli may be closed by collapse; to this extent the collapse is helpful and should be tried.

Another problem is presented in cases 2 and 5 in which there were no imperative anatomical indications for collapse. In one case the anatomical indication was in an extremely small minimal lesion; in the other, the indication was the atelectasis produced by the bronchial lesion but mistaken for pneumonia. In both cases the bronchial lesions were the source of the tubercle bacilli which could not be eliminated by collapse; and in both cases the bronchial lesions formed the major disease picture, while the pulmonary lesion appeared comparatively insignificant and was overshadowed by the effects of bronchial occlusion. In these cases, the collapse serves no useful purpose; and in case 2 it appeared to be actually harmful in that it helped to render cough ineffective. In both cases whole healthy lobes were kept in a constant state of useless collapse; and in case 2 a healthy lobe was converted into a mass of atelectasis and fibrosis. Therefore, when the anatomical indications are not compelling, collapse should not be used in the presence of ulcerative tuberculous tracheobronchitis. This leads to the suggestion that whenever collapse is undertaken primarily to eliminate persisting positive sputum, careful history and physical examination should be directed toward the study of the bronchial complication; and when the clinical suspicion of its presence is aroused, bronchoscopy should be used to confirm the diagnosis before embarking upon prolonged useless and perhaps harmful collapse.

*Results:* The results in nine cases with proven ulcerations have been as follows:

Dead: Four, three by suffocation. On admission, two were classified as minimal and two as moderately advanced pulmonary tuberculosis. Death occurred from nine to sixteen months after the diagnosis of ulcerative tuberculous tracheobronchitis was established by bronchoscopy. One was treated by unilateral pneumothorax, phrenic paralysis and intra-

pleural pneumonolysis, one had bilateral pneumothorax, two had no collapse therapy

Living Five On admission, two were classified as minimal, two, moderately advanced, and one, far advanced Two had complete collapse by pneumothorax, one of them had an adjuvant phrenic paralysis and intrapleural pneumonolysis, one had phrenic paralysis All are still under treatment from six months to two and one-half years after the diagnosis of ulcerative bronchitis was established by bronchoscopy None are ambulatory

### CONCLUSIONS

Ulcerative tuberculous tracheobronchitis exists as a complication of pulmonary tuberculosis with an unknown incidence

It forms a possible and probable mechanism for obstructive atelectasis and the likelihood of atelectasis is increased following pulmonary collapse measures

It is a probable source of tubercle bacilli in the sputum (1) in patients with little or no roentgen evidence of pulmonary tuberculosis, and (2) in patients with adequate collapse of the lung

The ulcerations and their symptoms, except under one condition, are not affected by collapse of the lung since the rigid bronchi may be shortened but not collapsed The exception to this statement is found when collapse produces bronchial obstruction, thereby preventing the passage of air through the stricture and so obliterating the symptoms

Collapse of the lung may be harmful, but reexpansion of the lung after collapse in our experience has been either impossible or harmful

The indications for collapse are affected by this complication as follows (1) Atelectasis, resulting from the complication, may be mistaken for tuberculous pneumonia and this taken as an indication for collapse (2) Collapse therapy is not contraindicated when the pulmonary lesion *per se* offers an early threat to life Diagnostic bronchoscopy does not affect the indications for collapse in this group (3) Collapse therapy is contraindicated when the chief indication for collapse is the control of sputum containing tubercle bacilli

Diagnostic bronchoscopy is indicated in group 3 to prevent useless collapse therapy

In the ulcerative form of tuberculous tracheobronchitis biopsy is harmful and bronchoscopy may be harmful Therapeutic bronchoscopy is indicated when necessary to relieve impending suffocation In our

present state of knowledge, bronchoscopy may be justified in many other instances as our only means of study

A rational program of therapy has not been determined

Our ideas have been in a constant state of evolution since our first contact with this complication seven years ago, this is to be regarded as a preliminary report

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# BRONCHIECTASIS<sup>1</sup>

## An Analysis of Its Causes

PAUL M. ANDRUS

Bronchiectasis is customarily attributed to a weakening of the bronchial wall by infection, together with a dilating force of one kind or another. Considerable uncertainty exists as to the probable nature of this latter factor. A variety of dilating forces have been proposed from time to time, but many of these are not consistent with the physical conditions known to exist within the thorax. All are controversial in terms of their relative importance and frequency of occurrence.

We have therefore attempted a systematic examination of the nature, value and direction of the various intrathoracic physical forces, in an effort to evaluate their relative probabilities as dilating agents. Although the approach is made primarily from the standpoint of physics, it has been necessary in addition to show to what extent the nature and occurrence of these forces agree with the known clinical and pathological characters of the disease.

Professor R. L. Allen of the Department of Physics of the University of Western Ontario has very kindly assisted in the preparation of the manuscript and concurs in the correctness of the physical considerations outlined.

### THE DILATING AGENTS

The following is a classification of the agents commonly cited as being capable of causing dilatation of bronchi. The physical mechanism of each of these will be examined in an effort to arrive at their relative probabilities as causative factors in this disease.

#### CLASSIFICATION OF DILATING AGENTS

##### I Ectasia from Within the Bronchi

A A gas-pressure effect due to (1) the negative pressure of the pleural space, (2) cough, (3) partial bronchial obstruction

B The pressure of secretion

<sup>1</sup> From the Mara Laboratory\* at the Queen Alexandra Sanatorium, London, Ontario

\* Assisted by the National Research Council of Canada

## II Ectasia from Outside the Bronchi

- A Retraction of fibrous tissue
- B The normal inspiratory dilatation of the bronchi (Inspiratory tug of the thoracic walls)
- C Pulmonary atelectasis

## III Congenital Bronchiectasis

## IV The Rôle of Infection in Bronchiectasis

- A The replacement-abscess hypothesis
- B Normal versus abnormal dilating forces

## I ECTASIA DUE TO FORCES OPERATING WITHIN THE BRONCHI

*A Gas-Pressure Effects*

## (1) Bronchial Dilatation from Gas Pressure Due to the Negative Pressure of the Pleural Space

Bronchiectasis is frequently explained as being due (when the walls are weakened) to the excess pressure of the intrabronchial gas over the subatmospheric pressure of the contents of the pleural space (1) (3) (4) It is commonly added that the abnormally negative intrapleural pressure that results from atelectasis aggravates this effect (5) (6) (7)

In the case of an aerated lung this is obviously not the case Under these conditions, the bronchi are neither surrounded by nor exposed to the pressure of the pleural space They are surrounded by respiratory air chambers in which the pressure during respiration is alternately higher and lower than that within the bronchi The bronchial walls are therefore not directly exposed to the pressure difference between their contents and that of the pleural space, and in the presence of an aerated lung this obviously cannot constitute an immediate dilating force

It may be reasoned however that such effects may be transmitted to the bronchi through intervening solid tissues This entire subject has been examined in detail in a preceding complementary communication (9) In this study it is shown that the difference in pressure between the contents of the lung and that of the pleural space is not so directed as to subject the pulmonary tissues to a corresponding mechanical stress It is necessary however to refer the reader to the above noted communication for the physical details

This situation then excludes the negative pressure of the pleural

space, normal or abnormal, as an agent in the production of bronchiectasis

## (2) Bronchial Dilatation from Gas Pressure Due to Cough

Cough is commonly considered to be an important agent in the production of bronchial dilatation (17) (18) (54) (58) (59) Miller (1) in discussing bronchiectasis states, "Compared with the force of hard coughing, such forces as may arise in thoracic traction or in massive collapse of the lungs are insignificant" Boyd (26) on the other hand describes the relationship as "highly problematical" and occasional other dissenting voices are heard (19) Other authors (4) (8) (60) consider that dilatation may result from the deep inspiration which precedes or follows cough rather than from the expulsive phase

The increased mechanical traction of the lung and thoracic walls upon the bronchi which results from full inspiration is examined in a later section (section IV, B) The present section is confined to the study of gas-pressure effects

Let us examine then the gas-pressure relations during the act of cough As shown in a previous communication (9), the lung is expanded mechanically by traction from the outward moving thoracic walls The gas pressure falls in the easily expansible respiratory air chambers, and air flows into them primarily from the relatively rigid bronchial reservoir During inspiration, then, the gas pressure in the bronchi is higher than in the peribronchial tissues, and this is therefore a possible dilating agent During expiration the pressure relations are reversed and the bronchi are exposed to a compensatory compressing force

Whether or not the normal physical stresses to which the bronchi are exposed are customarily sufficient to produce bronchiectasis, will be examined at length in a later section (section IV, B) We are here concerned with whether cough produces an *enhancement* of the normal pressure conditions such as to subject the bronchi to an *abnormal* dilating stress

The inspiration preceding cough is customarily more full and executed at a more rapid rate than is normal inspiration, that is, there is a greater flow of gas without corresponding increase of time This physical situation would in itself result in a greater than normal gas-pressure difference between the interior and exterior of the bronchi However, full inspiration is accompanied also by a *dilatation* of the bronchi (10), an effect not sufficient to be readily observable in normal respiration

A larger conducting channel is thus provided for the increased rate of gas flow. Poiseuille's equation shows that the rate of gas flow in a tube varies as the fourth power of the diameter. For example, if the diameter of a tube is doubled, the gas flow will on this account be increased  $2^4 = 16$  times. Thus a given increase in the diameter of a bronchus produces a largely disproportionate increase in its gas conducting capacity. Douglas and Haldane (53) have shown experimentally that the functional capacity of the respiratory air passages may be increased by nearly four times during moderate exercise.

This increased size of the conducting pathways must then compensate in whole or in part for the increased gas flow of deep inspiration. A significantly greater than normal gas-pressure difference between the interior and exterior of the bronchi is thus not shown to result necessarily from the deep inspiration preceding cough. As shown above, the bronchi are subjected to a compensatory compressing pressure during the expiratory phase of cough.

An assumption of an increased dilating stress upon the bronchi as a result of gas pressure during cough is thus apparently not warranted, or if present must be relatively slight and not in proportion to the increased gas flow.

It should be noted that the subjective sensation of "force" and "strain" which arises from cough is due largely to spasmodic contraction of the abdominal and other muscles. It is in this sensation that the above quotation from Miller presumably has its source. From the standpoint of the lung, this muscular stress is utilized to produce expiratory elevation of gas pressure. In a previous study (9) it was shown that this pressure may be so distributed as to cause peripheral pulmonary emphysema. From the foregoing considerations, however, it is apparent that the greater the pressure, the greater is the compressing effect upon the bronchi. Thus, great as the stress of continuous and hard coughing may be, it is not shown that this stress is so directed as to produce dilatation of bronchi. On the contrary it is so directed as to compress and protect them.

*Clinical correlation with cough.* From the clinical standpoint, although the disease is by some considered to result from chronic cough (chronic bronchitis) (41) (54) (61), the majority of recent observers do not assign any great frequency to this among the causative agents, but emphasize the pneumonic and pneumonia-producing diseases (2) (3) (4) (5) (14) (19) (21) (25) (42) (43) (58).

We may add our own observations on some two thousand exsoldiers of the district who are pensioned for chronic pulmonary disease which became manifest during the war period of 1914 to 1918. These subjects have been clinically reviewed with radiography when indicated, at two- to three-year intervals over a period in excess of fifteen years. Among these we have not seen an individual with idiopathic chronic bronchitis who developed apparent bronchiectasis over this period, except following an intercurrent pneumonia.

Thus the above conclusions that the physical stresses resulting from cough are not so directed as to produce bronchial dilatation, are in the main confirmed by clinical experience.

### (3) Bronchial Dilatation from Gas Pressure Due to Partial Fixed Bronchial Obstruction

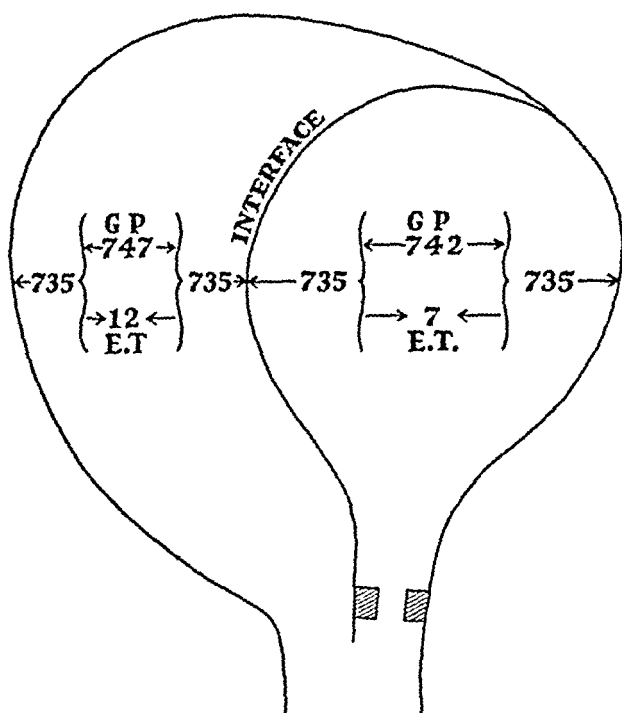
That bronchial obstruction plays an important rôle in bronchiectasis is claimed by practically all authors on the subject. Indeed the gross and rapid dilatation of bronchi distal to an obstructing tumor or foreign body is so impressive as to be convincing of an aetiological relationship (16) (18) (59). To study the expected physical effects upon the bronchi of a partial, fixed bronchial obstruction, it is necessary to examine the effects upon the related section of lung as a whole.

*Bronchial obstruction during inspiration.* The relative distribution of stresses during the inspiratory phase of respiration in contiguous obstructed and nonobstructed sections of lung is shown schematically in figure I. The arrows indicate the direction in which the forces operate. The values placed outside of the brackets are in each case the algebraic sum of the two directionally opposed forces shown within the brackets, namely the gas pressure ( $GP$ ), and the elastic tension of the lung ( $ET$ ).<sup>3</sup>

Consider first an inspiration commencing from a resting stage sufficient to permit the gas to flow to an equilibrium of pressure throughout the lung. As shown in a former publication (9), the outward movement of the peripulmonary walls results in a dilating traction simultaneously upon all the air chambers throughout the lung. The obstructed and nonobstructed sections of lung are thus subjected to equal initial expansile movements and consequent lowering of gas pressure. However, because of the retarded inflow of gas, the pressure will rise less rapidly

<sup>3</sup> The popular conception of elasticity as "ease of deformity with readiness of recovery of size and shape" is intended throughout the article.

in the obstructed section than in the remainder of the lung, and the surrounding lung will "bulge" into and encroach upon the gas-starved areas. The increased elastic tension resulting from this compensatory over-expansion will however prevent the gas pressure in the obstructed section from being raised to the same level as that of the surrounding lung, as would be the case in nonelastic sacs.



STRESS RELATIONS IN OBSTRUCTED AND NORMAL SECTIONS OF LUNG

FIG 1

Because the obstructed section is under-expanded, its elastic tension must also be subnormal. Since an obstructed section of lung operates at both subnormal gas pressure and subnormal elastic tension during the inspiratory phase of respiration, it would appear that it is specifically protected against mechanical injury at this period. The lower gas pressure however means a greater gas-pressure *difference* for the propulsion of gas past the obstruction. This will partially, but of course not completely, counterbalance the obstructing effect of the same.

The interface between obstructed and nonobstructed sections of lung

has of course no appreciable mechanical rigidity. This surface must therefore at all times promptly adjust its position until the stresses to which its opposite faces are exposed are in equilibrium (735 on each side in figure I)

It should be noted however that a bronchus is not situated as is the stem of a balloon, but is largely invaginated by the functionally related air cells as are the branches of a tree by its leaves. The peribronchial gas pressure is therefore that of the functionally related section of lung and not that of the contiguous normal lung. Since the *rate* of gas flow is slowed down distal to an obstruction, the gas-pressure difference between the interior of a bronchus and its surroundings will be *less* under these conditions than for the bronchi elsewhere. The bronchi of an obstructed section of lung would therefore appear to be still further protected against mechanical injury on this account.

During the inspiratory phase of respiration then, the dilating stresses, both by gas pressure and elastic pull to which a bronchus distal to a fixed partial obstruction is exposed, are less than those of the bronchi elsewhere. We must conclude that a partial fixed bronchial obstruction results in relative mechanical protection against dilatation of the related bronchi during the inspiratory phase of respiration.

This is however not the case for the bronchi elsewhere. The bronchi outside of the obstructed section of lung are exposed to the increased elastic pull of the generalized compensatory over-expansion. If the obstruction is high-grade, and if the volume of the obstructed section is large in proportion to the total lung, this over-stretching may assume important values. On a physical basis it is therefore logical to expect bronchial dilatation to occur in the surrounding lung rather than in the affected bronchus, when a partial fixed obstruction is present.

However, it is generally believed that weakening of the bronchial wall by infection is an important complementary if not a determinative factor in the production of bronchiectasis. Infectious injury, both as a cause and effect, is much more likely to be associated with obstructed bronchi than with those elsewhere in the lung. Unless the bronchi are weakened by infection, this compensatory over-expansion would be expected to involve chiefly the respiratory air chambers rather than the bronchi, that is, to consist of emphysema. As will be enlarged on later, this is in fact the observed effect.

In addition, as will be shown in a later section (see *Atelectasis* the distribution of elastic hypertension), the direction of this force is such as

to result for a given chamber, primarily in distortion of form, and not essentially in dilatation

*Bronchial obstruction during expiration* Let us now examine the sequence of events during expiration. As shown in the above noted publication (9), gas is normally expelled from the lung by the simultaneous contraction of the elastic elements throughout, when this is permitted by recession of the thoracic walls. A propelling movement by the thoracic walls is however available as a reserve measure chiefly during cough.

At the commencement of expiration, the lower elastic tension of the obstructed section of lung then implies a subnormal gas-propelling force as compared with the lung elsewhere. Infectious injury, which is apt to be localized because of obstruction, may be expected to lessen still further the elastic recoil of such a section. As expiration proceeds, gas will escape relatively more rapidly from the normal than from the obstructed section of lung. The normal part of the lung may therefore be expected to recede from its position of encroachment on the obstructed section, and eventually a point will be reached at which the gas pressure and elastic tension of the two parts will become equalized.

Thus, from the above considerations it is clear that the force normally utilized in the propulsion of gas past an obstruction in a bronchus is greater during inspiration (greater gas-pressure difference), and is less during expiration (lesser elastic tension), than for the remainder of the lung. From this situation, an accumulation of gas in the obstructed section of lung *in proportion to the size of the bronchial aperture* may then be predicted.

Prior to reaching this point of equilibrium of stresses then, there is a *relative* increase in the volume of gas in the obstructed section in *proportion* to the size of the aperture. The *actual* amount of gas in the obstructed section of lung will however necessarily be subnormal. Subsequent to this point of equilibrium the physical stresses will be the reverse of those previously existing, that is, the section of lung having fixed, partial bronchial obstruction may be over-distended, and operate at a higher gas pressure *as compared with the remainder of the lung at that time*. The excess of gas in the obstructed section will be dissipated during the resting stage which normally follows expiration, or, failing this, the inflow of gas in the ensuing inspiration will be delayed until equilibrium with the rest of the lung is again attained. The over-distention could not be continuous as proposed by MacCallum (8).



The question then arises whether it is possible for this *relative* over-expansion of an obstructed section of lung to become an *actual* over-distention and expose the tissues to mechanical injury. The physical considerations outlined however indicate that, in the presence of a partial fixed bronchial obstruction, the related section of lung at all times contains less than its usual or normal supply of gas. If respiration were suspended for a material period of time at the end of inspiration, a partially obstructed section of lung could acquire its full or normal complement of gas. An actual or absolute over-distention of the section would then be expected to result during the ensuing expiration. Such a suspension of respiration however does not seem to occur other than voluntarily, and its frequency must therefore be low.

An interpretation of over-distention and consequent injury to tissue in a section of lung as a result of a partial, fixed obstruction of the related bronchus, therefore, does not seem to be warranted on a physical basis, rather the reverse is shown to be the case, a section of lung so exposed being specifically protected against injury by over-distention during both the inspiratory and expiratory phases of respiration.

*Valvular bronchial obstruction.* A number of authors specify or imply that a valvular action may prevent exit of air to a greater extent than inflow, and thus cause bronchial dilatation (2) (4) (5) (8) (15) (16). The term is usually loosely and vaguely used without specific attempt to show a physical basis for a one-way obstruction. Foreign body, tumor, aneurism, kinking, secretion and enlarged lymph nodes as well as functional effects are mentioned as agents which might produce this effect. Such valves may be considered in groups as follows:

(a) Aneurism, extrabronchial neoplasm, or enlarged inflammatory lymph nodes, might conceivably from vascular and respiratory movements cause a valvular pressure upon the walls of a large bronchus. Gross over-distention of a lung has on occasion been observed under these conditions. The frequency of such a process must however be very small and is thus a negligible agent as far as bronchiectasis is concerned.

(b) Bodies which are moveable within the lumen of the bronchus, such as foreign body, pedunculated tumor, or free secretion. Such a body during inspiration might move to, and be arrested at, positions of normal bronchial narrowing, such as the mouths of smaller tubes or the normal tapering of the bronchi, and be moved away from this position by the expiratory outflow of gas. Such a valve would however limit the in-

flow of air, and favor its exit—that is, would operate to empty and not to over-distend the related section of lung.

(c) However, when an *eccentric* fixed partial obstruction exists, such movable bodies, distally placed, might well exert a valvular action in the opposite direction. Thus in inspiration the flow of gas could move such bodies away from the opening, favoring the inflow of air, while the expiratory flow might lodge a movable body (such as secretion) in a narrowed aperture, causing greater obstruction during this phase.

Such an over-distention of lung is actually seen when a peanut becomes lodged in a bronchus. It would not be expected however that such a physical state would be sustained for any great length of time. In the presence of an obstruction sufficiently great to arrest the expulsion of secretion, exudation would be accelerated, and complete obstruction and atelectasis would be expected to result soon. Thus, although over-distention of a section of lung is possible under these conditions, the frequency and probable duration of such a process is such that it must be classed among the rarer possible causes of bronchiectasis, and its effects might readily be confused with those of atelectasis.

(d) A further type of valve may be proposed to arise from kinking of a bronchus during the respiratory movements, or from buckling of a layer of secretion during the changes in the length of bronchi in respiration. Under these circumstances however, the *mean* size of the bronchial aperture would be the same during inspiration as during expiration. In other words, the valve would operate equally in both directions and therefore have the effect only of a fixed partial obstruction.

The ball-valve proposed by Warner (2), where the lumen is obstructed but the respiratory changes in size of the bronchus continue, is of this same type, that is, the mean size of the aperture would be the same in inspiration as in expiration and the valve would operate equally in both directions.

(e) Warner (2) also states that "Central bronchial obstruction has its greatest effect in causing bronchial dilatation during coughing." This would constitute a functional valve. This would be true if respiration were suspended at the end of the inspiration preceding cough, allowing time for the obstructed section of lung to acquire its full quota of air. The expiratory phase of cough would then over-distend this section in proportion to the rest of the lung, because of the impeded outflow of air. Without such suspension of respiration, the resulting

over-expansion is as shown for a fixed bronchial obstruction, *relative* in proportion to the size of the aperture, but not *absolute* in proportion to the normal capacity of the section of lung

Since such suspension of respiration is not customary, we conclude that specific injury from cough in the presence of partial bronchial obstruction is also not shown to be of significant frequency

(f) Localized muscle spasm as from the irritation of a foreign body or ulcer might conceivably exert a valvular effect. Such an irritable focus would be expected to be particularly stimulated, and the spasm most pronounced, as a result of the stretching effect of the inspiratory movement. Such a valve might therefore be expected to limit the inflow rather than the outflow of air

(g) MacCallum (8) and others (24) propose that the active forces of inspiration as compared with the passive forces of expiration produce a functional expiratory valve in the presence of a fixed partial bronchial obstruction. That this is not the case has been shown at length in a preceding section (I, A, (3) Expiration)

We may add that there is no physical reason why such a situation should produce a valvular effect in the presence of obstruction any more than in a normal bronchus

In conclusion we are unable to determine a physical mechanism by which a valvular retention of gas may other than occasionally be expected to result in over-distention of the related section of lung

*Clinicopathological correlation of partial bronchial obstruction* Since bronchial dilatation is a conspicuous accompaniment of obvious bronchial obstruction (foreign body, tumor, etc.), the above physical conclusions create an apparently anomalous situation. We are faced with the alternative conclusions: first, that something has been overlooked in the physical situation, or second, that the observed dilatation is caused by further associated factors

Two classes of bronchiectasis may be examined: first, those with obvious obstruction, and second, those in which obstruction is not identified

When bronchiectasis distal to obstructing tumor or foreign body is seen at autopsy, the condition when recognized during life is identified by the radiographic exhibition of regional atelectasis. This means that the bronchial obstruction has been complete and not partial (12). A narrow channel may conceivably be obstructed either continuously or intermittently by mucous or oedematous mucous membrane, though readily admitting the passage of a metallic sound at autopsy. The

completeness of the obstruction may thus be readily overlooked. It is notable that the types of foreign body especially mentioned and illustrated in textbooks of pathology as causing bronchiectasis are those which swell when wet, and are mechanically adapted to cause adhesion of secretion, namely, beans and twisted string.

Thus bronchiectasis resulting from obvious bronchial obstruction may from the clinicopathological standpoint be at least as well explained on a basis of atelectasis as of partial bronchial obstruction. The physical effects of atelectasis will be enlarged upon in a later section, but we may say in anticipation that the physical stresses resulting from this agent provide the most satisfactory explanation of bronchiectasis of any of the causes currently proposed.

Obvious obstruction as above, of course, explains only a small percentage of cases of bronchiectasis. Because of the conspicuousness of dilatation when bronchial obstruction is gross and obvious, many authors have concluded that lesser degrees of obstruction, as by inspissated exudate, may be a cause of otherwise idiopathic bronchiectasis.

Bronchiolar obstruction may result from pneumonic exudate and produce atelectasis as discussed later (32). It is difficult however to conceive of a mechanism by which a number of large bronchi in both bases may simultaneously undergo an important degree of obstruction, and this is necessary in order to support such a hypothesis. That dilated bronchi are obstructed bronchi is well known (5) (14). When the bronchi and related lung have suspended function, an accumulation and inspissation of secretion may be understood, but this appears to be more logical as an effect than as a cause of dilatation. Again the diseases characterized by chronic purulent expectoration, that is, bronchitis and tuberculosis, in no way provide a reservoir from which the clinical bronchiectatic material specifically appears.

Thus there is nothing in the known clinicopathological characters of bronchiectasis to indicate that the previously noted physical conclusions are not correctly conceived.

From the physical, clinical and pathological considerations involved we therefore conclude: (a) That partial bronchial obstruction is not shown to result in physical forces which may produce dilatation of the affected bronchi; and (b) that the dilatation observed to occur distal to bronchial obstruction is satisfactorily explained only on a basis of complete obstruction and atelectasis, and not as a result of a partial bronchial obstruction.

These conclusions must not be interpreted as minimizing the possible effects of bronchial obstruction as an agent in the furthering of infectious injury by interference with drainage. They relate only to the mechanical dilating forces concerned.

### *B. Bronchial Dilatation from the Pressure of Contained Secretion*

Although pressure from contained secretion has been cited as a possible cause of bronchial dilatation (17) (18) (52) (54) (55) (65), other recent authors on the subject think that such a force is probably insufficient to produce this effect (2) (8).

As a problem in physics it is sufficient to note at this time that in order to exert a dilating force it would be necessary that the secretion first completely occupy the cross section of the lumen of the bronchus. Such a condition would however necessarily result in atelectasis, and its possible effects be indistinguishable from those of the latter. Further consideration of the subject will therefore be deferred to a later section dealing with the physical effects of pulmonary atelectasis.

## II FISTULA DUE TO FORCES OPERATING OUTSIDE THE BRONCHI

### *A. Bronchial Dilatation Due to Contraction of Fibrous Tissue*

Retraction of scar tissue is commonly cited as a cause of bronchial dilatation. The majority of authors regard it as an important cause along with other agents (4) (11) (14) (16) (17) (20) (58) (59) (60) (65). Findlay and Graham however assign it "the chief—if not the sole" rôle, in the causation of this disease.

The source of these conclusions is presumably the frequent demonstration of conspicuous scar tissue in autopsy material, as well as irregularities and dislocation of adjacent organs as seen in radiographs.

Dissenting voices are, however, raised with increasing frequency as indicated by the following quotations. MacCallum (8), "cannot be a general explanation," Warner (2), "rarely if ever the primary cause," Corvillo (1, discussion), "irrational." Other authors describe the development of bronchiectasis in the absence of fibrosis, and with a rapidity which precludes fibrosis as a reasonable cause (3) (5) (21) (32). Hoover (19) doubts the importance of fibrosis as a causative agent because dilatation does not regularly follow when this is present. Kautmann (18) records that bronchi within contracting lung tissue are "compressed and become obliterated."

Let us examine the problem then from the standpoint of the expected physical effects upon a section of lung, of the development of fibrous tissue. Specifically we have to consider first, whether contraction of fibrous tissue may be so directed as to pull the opposite walls of a bronchus away from each other, that is, to dilate them; and second, whether fibrosis, as is sometimes stated (2), results in an enhancement of the value of the normal respiratory pull upon the walls of the bronchi.

In the first place, if a section of lung undergoes generalized shrinkage in volume as a result of fibrotic contraction, it is apparent that the contained bronchi may participate in the general reduction in size. In any event the shrinkage means that the fibrotic contraction has more than overcome whatever dilating stresses are in operation, and the contained bronchi are therefore specifically protected against dilatation on this account.

If, however, two opposite faces of a continuously fibrotic section of lung are anchored to supports having sufficient rigidity to resist dislocation by the pull of fibrotic shrinkage, the situation may be different. Under these circumstances the walls of the contained bronchi are exposed to the outward pull of the fibrotic shrinkage and dilatation may result from this cause. Continuity of fibrotic tissue and rigidity of anchorage at opposite faces are therefore essential to the production of these conditions. Thus an intervening section of normally elastic lung would destroy the necessary rigidity of anchorage and create a different physical situation as examined later. The diaphragm and the more mobile parts of the bony walls are known from clinical observation to be readily susceptible to inward dislocation. They do not therefore offer anchorage of sufficient rigidity to fulfill the above conditions. Sufficient rigidity of anchorage may however be conceived as possible between the lateral surface of the spine and the relatively rigid and immobile posterolateral thoracic wall. As shown in a former publication<sup>1</sup> (9), the normal forces by which the two layers of the pleura are maintained in position provide more than ample anchorage for the purpose, and it is unnecessary to stipulate the presence of interpleural adhesions. The direction of this axis of anchorage is at right angles to the bronchi at the base and this is the common seat of bronchiectatic disease.

On a physical basis, bronchiectasis of this region may thus be reasonably explained as possible from contraction of fibrous tissue. Whether the necessary continuity of fibrotic tissue commonly occurs across the complete width of the bases is however less clear. The literature of

recent years has emphasized that the most common cause of widespread fibrosis is pulmonary atelectasis (13) (20) (22) (23) (24) (25) (38). However, when a single lobe of a lung becomes atelectatic, it collapses towards its medial attachment at the hilum, and withdraws from the thoracic wall, this space being reoccupied by the elastic tissue of another lobe. Thus, under the conditions most likely to produce a fibrosis of sufficient extent to fulfill the necessary conditions, the continuity is interrupted by withdrawal of the affected lung from its position of anchorage.

We have next to consider whether fibrosis may be expected to alter for better or for worse, the pull exerted upon the bronchi by the normal inspiratory movements. If lung is infiltrated with fibrous strands, the elastic tissue offers increased resistance to expansion—that is, to attain a given increment of expansion a greater tractile force would be necessary than in the case of normal lung, or conversely a given force would produce less expansion. For a given amount of respiratory movement, elastic tissue so splinted would be in the position of a more powerful spring, that is, it would exert greater pull than the normal lung. Providing the splinted elastic were not so over-stretched as to prevent recovery of its original length on release, (that is, the elastic limit were not exceeded), this situation would result in an abnormal dilating stress upon the bronchi. However the recovery of an elastic so splinted would be expected to be also impaired. We know from clinical experience that pulmonary disease very promptly results in localized respiratory lag. Thus this is observable in the region of tuberculous or pneumonic infiltrations known to be of very short duration. It seems very probable that the amount of respiratory excursion at any region is automatically limited by the resistance offered to this movement, that is, that in involuntary respiration the thoracic walls move outward until the usual value of resistance is reached, and that movement is suspended at that point. At any rate we know that the amount of excursion is promptly and materially lessened when pulmonary elasticity is splinted. Such lessening must, at least in part, and possibly wholly, protect the related lung from the increased stress which would otherwise result from fibrotic infiltration.

As before, however, such potential increase in stress can be expected to be more or less completely compensated by lessening of the amplitude of the local respiratory excursion

From the clinical standpoint, bronchiectasis is customarily of rather acute onset. Progression of the disease is usually by a series of acuties rather than by gradual retrogression. Neither of these considerations fits well with the concept of a frequent origin in fibrosis. As above noted, observers of early pathological material report bronchiectasis in the absence of fibrosis.

Thus, in conclusion in general it seems probable that pulmonary fibrosis is more apt to protect the bronchi than to subject them to dilatation. Also it is shown that the effects of fibrosis may very readily be confused with those of pulmonary atelectasis. The possibility of bronchial dilatation resulting from pulmonary fibrosis is admitted, but it is not clear on either a physical or a clinicopathological basis that this is probably frequently the case.

#### *B Bronchial Dilatation Due to the Normal Inspiratory Dilatation of the Bronchi*

A physiological dilatation of the bronchi is observable with full inspiration both by bronchoscopy, and by radiography following the instillation of lipiodol (10). Warner (2) (5) points out that this force is so directed as to produce permanent dilatation of bronchi when their constrictor properties are injured as by infection. The consideration is important and has apparently been overlooked by previous contributors. The thoracic wall traction of other authors (18) (49) (58) is however part of the same process (9).

That this physiological dilatation is brought about by traction from the outward moving thoracic walls exerted through the parenchyma of the lung, and not by gas pressure, has been shown in a former publication by this author (9).

Whether this normal force is with any frequency sufficient to produce dilatation of bronchi is however an open question. Since a further school of thought has proposed that bronchiectasis is purely a destructive process and that no mechanical dilating force is necessary, an examination of the relative merits of normal and abnormal dilating forces would seem to be premature, pending a decision as to the probable need of *any* dilating force. Discussion of this situation is therefore deferred to a final section, (section IV).



### C. Bronchial Dilatation Due to Pulmonary Atelectasis

The importance of atelectasis as an agent in the production and healing of pulmonary diseases in general, is receiving rapidly increasing attention in the literature. The majority of recent contributors on the subject of bronchiectasis list atelectasis among the important causative agents.

We have, however, seen no satisfactory explanation of the physical conditions which are credited with producing this effect. An examination of the same will therefore be undertaken here.

*The physical basis of atelectasis:* Atelectasis is identified radiographically by the displacement of organs toward areas of nonaerated lung. This displacement affords us an immediate clue as to the nature of the physical changes which result from atelectasis. The essential physical change that occurs when a portion of lung is collapsed is in effect a removal of a portion of that lung. This of course results from obliteration of some of the air chambers that formerly constituted a portion of its volume. This "lost space" must of course be reoccupied by adjoining structures. Hence the displacement of organs so characteristic of the condition.

This replacement may be effected from intrathoracic or from extrathoracic sources or from both, depending upon the relative resistance to dislocation offered by the parts. The bony walls of the thorax are too rigid to permit of more than mild compensatory collapse. The lost space may however be occupied by an elevation of the diaphragm. If air is admitted into the pleural space, this also may compensate for pulmonary volume lost through atelectatic collapse.

If, however, compensation is not completely effected through these agencies, the only possible alternative is an over-expansion of the remaining pulmonary tissue to occupy the lost space. This may rise to considerable values and is continuously exerted; and this increase in elastic tension represents the *new* intrathoracic force that comes into play when atelectasis is present.

*Physical evidence of elastic hypertension with atelectasis:* In addition to the anatomical observations above mentioned there are several physical phenomena associated with pulmonary atelectasis which clearly indicate the presence and force of associated elastic hypertension.

The intrapleural pressure The chief of these is, of course, the abnormally negative pressure in the pleural space

The normal negative pressure of the pleural space is caused by and is a direct measure of, the elastic recoil of the lung (33) Conspicuous increase in the negativity of this pressure is emphasized by practically all contributors on the subject of atelectasis, (1, discussion by Hedblom) (4) (5) (27) (34) (35) (36) (37) (38) These observers record negativity as high as 100 cm of water being twenty times that of the normal resting stress

Abnormally high negative pressures are an every-day event to those administering pneumothorax therapy to the tuberculous In inducing pneumothorax it is not rare to see the water aspirated from the manometer arm, indicating for the commonly used instruments a negativity of pressure in excess of 50 cm of water

The author examined the initial pressures in fifty consecutive cases of successfully attained artificial pneumothorax where dislocation of organs was visible in the original chest radiographs, and a further fifty cases in which such dislocation was not visible The average figure for the cases in which dislocation of organs was not visible was  $-4-8$  cm water The average figure for the cases in which atelectasis might be inferred because of visible dislocation of organs was  $-8-16$  cm water An average of double the normal pulmonary tension was thus seen for the group having evidence of possible atelectasis

Since the normal negative pressure of the pleural space is known to be caused by the elastic tension of the lung, the abnormally negative pleural pressures of atelectasis must indicate a correspondingly increased elastic tension under these conditions

It should be noted that these values represent, not the initial force resulting from atelectasis, but only the residual force after presumably partial compensation has occurred from outside sources Again the stress indicated by pneumothorax pressure is a mean value for all directions As will be shown in a following section, a localization of stresses greatly in excess of the mean value occurs when pneumothorax is not present

*Other physical evidences of elastic hypertension of the lung in the presence of atelectasis* There are other physical phenomena observable when atelectasis is present which are explainable only on a basis of elastic hypertension and not as gas-pressure effects These are the pendulum movement of the mediastinum, the paradoxical movement of the dia-

phragm; and that very good friend of the pneumotherapist, selective collapse. Limitations of space however do not warrant a detailed enlargement of these physical effects at this time, as the existence of elastic hypertension in the presence of atelectasis is abundantly demonstrated by the considerations of the preceding section.

In addition, compensatory over-expansion of the remainder of the lung has been recorded as both a direct pathological and radiographic observation when atelectasis is present (18) (29) (31) (32).

*The physical effects on the lung of elastic hypertension:* As shown in the preceding sections, the essential change which results when a portion of lung is collapsed is a compensatory over-stretching of the remaining normal lung. Such over-stretching necessarily constitutes an abnormal dilating pull upon all the air chambers involved; that is, both respiratory air sacs and conducting tubes.

The injury which may result from such a stress will depend upon two factors, namely the localization of the force, and the relative ability of the chamber walls to resist it. It is thus first necessary to examine carefully the *distribution* within the thorax, of the elastic hypertension which results when a section of lung is collapsed.

*The distribution of elastic hypertension:* When a section of lung is collapsed, its dimensions are shortened in all three planes. Compensatory replacement must therefore also be effected in three directions. Elevation of the dome of the diaphragm may replace the shortening in the vertical dimension of the lung, in whole or in part. The anteroposterior and lateral dimensions of the pulmonary cage however remain essentially unchanged. In these planes then the loss in pulmonary dimension can be replaced only by an over-expansion of the remaining lung in these directions.

Over-expansion of lung in the anteroposterior plane results in no readily observable effects. Over-expansion in the lateral plane may however produce conspicuous effects, namely dislocation of mediastinal structures to the affected side. Such displacement is of course due to over-stretching of the shortened elastic, and is not a gas-pressure effect as has been stated (35).

It is important to recognize also that mediastinal shifting does not provide *relief* from the stress arising from atelectatic collapse, but constitutes only an *equalization* of the stress between the two sides.

The quantitative distribution of these stresses is shown schematically in figure II. The cross-lined area represents a collapsed lower lobe.

The position and direction of the maximum abnormal pull is indicated by the arrows marked A, being the situations where shrinkage of the atelectatic section must result in an uncompensated over-expansion of the remaining lung. At the positions marked B, the over-expansion may be at least partly relieved by an upward dislocation of the dome of the diaphragm, and the abnormal stress be thus intermediate or slight.

### DIRECTION OF STRESSES WITH ATELECTASIS

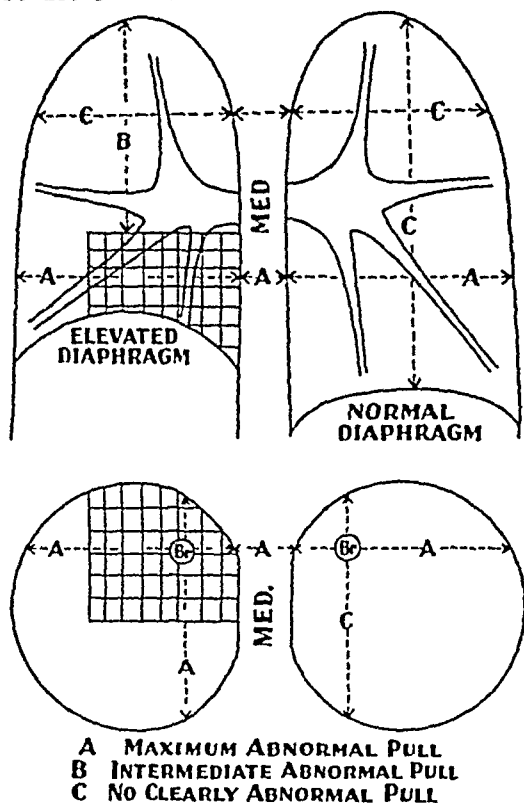


FIG II

in value. At the positions marked C no direct pull results from the atelectatic shrinkage, although some component of these forces can be presumed to be operative at all positions and directions throughout both lung fields.

The maximum pull resulting from atelectasis is thus seen to occur in all directions in the horizontal plane in the collapsed section of lung. For the lower lobe this force is essentially at right angles to the long axis.

of the lower lobe bronchi, and is thus concentrated as to site, and focused as to direction, at the position where bronchial dilatation most commonly occurs. It will be noted that elevation of the dome of the diaphragm lessens the dilating stress upon bronchi the main axis of which is horizontal, but affords no relief to the more vertically placed basal bronchi which are in fact the ones most commonly involved.

At the opposite base (when the mediastinum is moveable) and in the lung surrounding the collapsed lobe, the resulting pull at any point is primarily in one direction only. It may thus be expected to result essentially in dislocation and distortion of the bronchi of the part, although having also a lesser dilating effect. Only in the atelectatic section do the deforming forces operate simultaneously in *all* directions, that is, constitute primarily and entirely a dilating stress. Above the level of the collapsed section, no clearly significant new stress arises.

Thus it is seen that atelectasis may result in a concentration and focalization of powerful dilating stresses upon the bronchi of the affected region.

These considerations also indicate that section of the phrenic nerve can only partially relieve the elastic hypertension resulting from atelectasis, and that the relief so attained is not in the direction to protect the basal bronchi. Complete relief in all directions is possible only by the attainment of pneumothorax.

*Effects of elastic hypertension on the bronchi:* As above mentioned, both respiratory air chambers and conducting tubes are equally exposed to this dilating force when present. Infectious injury of the bronchial wall however may be presumed to be much more likely to be present, both as cause and effect, in the collapsed than in the normal sections of lung.

The bronchi in an atelectatic section of lung are thus specifically and selectively exposed to simultaneous weakening by infection, and a gross abnormal dilating stress. As reviewed in a later section bronchial dilatation is clinically a most conspicuous and constant accompaniment of lobar atelectasis. Here then for the first time is a completely satisfactory physical explanation of bronchial dilatation.

In the case of normal tissues, however, the bulk of the over-expansion would be expected to occur in the respiratory air chambers, because these are microscopically thin-walled and flexible. It is important to recognize however that this over-expansion of the pulmonary parenchyma in no way relieves the tension to which the part is exposed,

unless rupture of a number of air cells occurs. The bronchi may thus continue to be exposed to a very powerful and directionally focused dilating stress. It seems possible that their tonic properties may become exhausted by the continuity of the abnormal pull, and that dilatation may follow in normal bronchi. In fact Kline (42) records that in atelectatic bronchiectasis "Little or no involvement of the muscle and elastic tissue of the bronchial walls may be detected." This may also be the origin of the recorded cases of "dry," that is, uninfected, bronchiectasis, and of those cases that are symptom-free until haemoptysis occurs.

*Effects of elastic hypertension on the air cells. Emphysema in bronchiectatic disease.* It has already been pointed out that the bulk of the compensatory over-expansion which results when a portion of lung becomes atelectatic must at least primarily be borne by the respiratory air chambers. It is not to be expected however that the pulmonary elastic could for any very great time sustain such an over-extension (8). Thus unless the atelectasis is "cured" by a reopening of the conducting air channels, or the strain is completely relieved by a compensatory inward dislocation of the peripulmonary walls, the pulmonary elastic must eventually undergo either degeneration of elasticity, or must rupture. Thus, on a physical basis, emphysema would be expected to be the most common injury to result from sustained atelectasis.

There is abundant evidence to indicate that this is actually the case, and the close association of emphysema with bronchiectasis has not in our opinion been accorded the recognition which its frequency and importance warrant. Thus the earliest descriptions of the radiographic appearance of bronchiectasis was that of a "honey-comb" effect (14) (16 and references). Later it was found that less conspicuous ovoid and annular high lights at the bases, gave a good clinical correlation with bronchiectatic disease, and such shadows came to be interpreted as due to dilated bronchi. With the advent of lipiodol, however, it was found that dilated bronchi are only rarely visible without its use. Lipiodol does not customarily enter the ring-like shadows visible in the plain X-ray film and it is concluded that these are of air-cell and not bronchogenous origin, that is, are due to emphysema.

Because of the focalization of stresses as previously outlined, emphysema would be expected to be most pronounced in the lung in the immediate vicinity of atelectasis and bronchiectatic disease. As indicated above, this is distinctly the case. In this coincidence of clinical occur-

rence and anatomical position, we have an entirely satisfactory explanation of the early misinterpretation of emphysematous rings as dilated bronchi. As a matter of fact, the visualization of this type of shadow in association with patchy or lobar airlessness is still the best radiographic index by which the bronchiectatic type of disease is suggested.

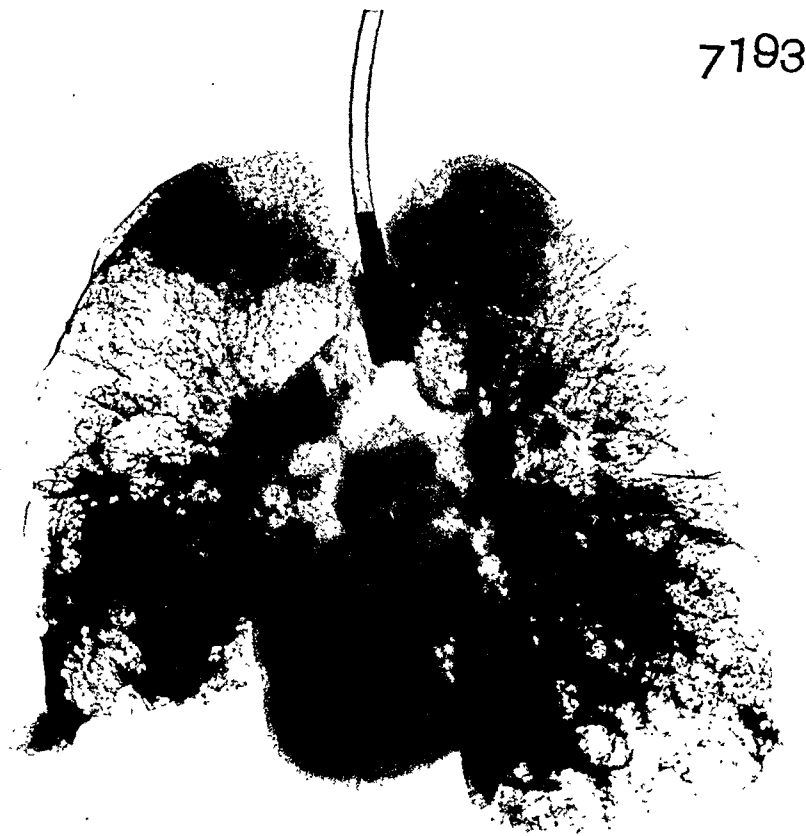


FIG. III. For description see text

Again it is common to see conspicuous ring-like shadows in the presence of clinically characteristic bronchiectatic disease, but no bronchial dilatations be demonstrable by the use of lipiodol. Here we may be dealing with the end-results of pulmonary infection and atelectasis, where the bronchi successfully resisted the dilating stress. However, we have seen bronchiectasis at autopsy where a recent apparently well-placed injection of lipiodol did not identify the dilatations, as well as

frequent negative lipiodol findings in entirely characteristic clinical cases, that is, with extensive offensive expectoration and decantation Boyd (14) emphasizes that dilated bronchi as seen with the bronchoscope are often obstructed by secretion and swelling Both radiographically and at autopsy gross emphysema may completely overshadow the bronchial dilatation Figure III is a typical radiograph of this type from an individual having extensive and very offensive expectoration Microscopically the ring-like shadows were seen to be of emphysematous origin

The association of emphysema with bronchiectasis and atelectasis is referred to by a number of authors, (8) (13) (16) (18) (48) (56) (58) (64), but as above noted the relationship is not customarily stressed One of these (Hewlett) states, "Bronchiectasis also arises in connection with emphysema and is merely an extension of that condition," and another (Green), "The causation of bronchiectasis is in great measure analogous to that of emphysema " With these statements, we are in full agreement Thus although bronchiectasis means only dilatation of bronchi, bronchiectatic disease as it actually occurs is so frequently a combination of bronchial dilatation with severe air-cell dilatation of common origin, that we propose that the term *Pulmonectasis* be used as more accurately descriptive of the basis of this type of disease Neither the aetiological nor clinical features of what is commonly called bronchiectasis are necessarily dependent upon the presence or otherwise of mere bronchial dilatation The disease is a chronic septic pulmonitis (1) (43) (43 discussion by Lord) with usually ectasia of both respiratory air chambers and conducting tubes A nomenclature of the disease which depends upon success or otherwise in demonstrating dilated bronchi is both artificial and misleading

*Atelectatic collapse of bronchial wall from gas pressure* There is, however, in addition to elastic hypertension, a further physical mechanism by which atelectasis may result in bronchial dilatation

Suppose a bronchus to be imbedded in pneumonic consolidation If the exudate were to be absorbed from a limited volume of alveoli adjacent to a bronchus while the bronchioles remained plugged, atelectatic collapse of the section would necessarily result If the rigidity of the surrounding pneumonic consolidation exceeded that of the bronchial wall, atmospheric pressure would push the latter into the "newly created space " If the surrounding consolidation lacks this excess rigidity, the collapse will occur from the pulmonary instead of the bronchial side



This may well be a cause of saccular bronchiectatic dilatations. We have no means of estimating the probable frequency of such an occurrence but it may well be frequent and important.

*Clinicopathological correlation of atelectasis and bronchiectasis:* That lobar atelectasis, single or multiple, is with a very high frequency accompanied by gross dilatation of the contained bronchi is generally recognized (2) (3) (6) (27) (29) (30) (31) (32) (50). Such terms as "invariably" (6) and "pathognomonic" (31) appear in the literature in defining this relationship. A major relationship is also described by many authors when atelectasis is recognized though not defined as lobar (4) (7) (16) (18) (24) (28) (42) (51) (56) (60). The clinicopathological correlation of bronchiectasis and atelectasis, when the latter is observed to be present, is thus greatly superior to that of any dilating agent proposed. In fact it is the only relationship which is not highly controversial.

However, although the relationship of lobar atelectasis to bronchiectasis is a very striking one, the former is not identified in any very high percentage of cases. Since we have concluded in the foregoing sections that the various other agents commonly held to be causes of bronchiectasis are unsatisfactory explanations of any important percentage of the same, we are left with a large group of cases which on this basis can be classed only as obscure or idiopathic.

Atelectasis being the only completely satisfactory and undisputed agent to which bronchiectasis is currently attributed, it is legitimate to consider whether this may account for still further cases in this otherwise unexplained group. The following considerations are pertinent to the examination of this question:

(a) It is not necessary that atelectasis be lobar in order to result in bronchial dilatation. The physical situation as outlined in this paper indicates that a given volume of pulmonary collapse should be equally effective in producing dilatation, whether it is lobar or patchy in distribution. Patchy atelectasis might however be expected to follow much more easily and frequently pneumonic processes than would a complete lobar collapse.

(b) The literature of recent years shows clearly that atelectasis is coming to be recognized as of great frequency and importance in the development and healing of pneumonic diseases of all types. Limitations of space do not warrant a detailed examination of these data here, but the

following references make this point clear (3) (12) (13) (20) (23) (27) (34) (36) (38) (40) (44) (45) (46) (47)

(c) Bronchiectasis is generally admitted to have characteristically its clinical origin in the pneumonia-producing and thus atelectasis-producing class of diseases (1, discussion by Coryllos) (2) (3) (4) (5) (14) (15) (19) (21) (25) (42) (43) (58) (59) Strumpell (58) states, "An acute pneumonic origin can be traced in all but a small proportion of cases of bronchiectasis "

(d) Patchy airlessness as seen in radiographs of the chest is so constant and conspicuous a feature of the bronchiectatic type of disease as to be one of the chief characters by which this condition is recognized Murr (60) states, "In adults, saccular bronchiectasis is nearly always associated with a local interstitial pneumonia with condensation and contraction of the lung tissue "

(e) The frequent association of conspicuous fibrosis with bronchiectasis in pathological material has led to a general assumption of a causative relationship However fibrosis is coming to be recognized as most pronounced as a *result* of atelectasis (13) (20) (22) (23) (24) (36) Thus Hennell (20) states, "The marked pulmonary fibrosis which develops after atelectasis occurs, eventually dominates the picture," and Hamman and Sloan (23) in discussing the pathological anatomy of collapsed lungs state, "The most striking change is the extreme fibrous tissue formation, this occurs in a degree never observed under other conditions " It would therefore seem that the frequent demonstration of fibrosis in the presence of bronchiectasis may be an indicator of the frequent association of atelectasis

(f) Atelectasis may conceivably produce bronchial dilatation but be subsequently dissipated in whole or in part (1, discussion by Coryllos) (3) (32) (36) We have personally observed alternate collapse and re-expansion of atelectatic lobes

The pneumonia-producing and thus atelectasis-producing class of diseases, which are so intimately associated with the onset of bronchiectasis, are rarely examined radiographically during the acuity The occurrence of atelectasis at this period is thus not customarily subject to observation

(g) Atelectasis has come to be recognized as a constant and integral part of the development and healing of pulmonary tuberculosis (references as under (b)) Dilatation of the regional bronchi would therefore

be expected to be common, as infectious injury is also regularly present. This is described as being the case in many pathological descriptions of tuberculosis (24) (26) (42) (59) (60) (66). Osler (59) states, "It is rare to dissect a lung in the chronic ulcerative form (of P.T.) without finding somewhere a dilated bronchus."

(h) Warner (5) states, "We have never observed a definitely bronchiectatic bronchus . . . where the lipiodol appeared to enter the parenchyma . . .," and Salkin and coworkers (66) in their reports on post-mortem bronchography ". . . the alveoli dependent upon these dilated bronchi did not fill with the dye." This is clearly evidence of customary airlessness of the functionally related air chambers.

These considerations individually and collectively may then be fairly interpreted as indicating that the frequency of atelectasis as an antecedent of the bronchiectatic type of disease probably grossly exceeds its customarily recognized occurrence.

When therefore it is considered, first, that atelectasis is much the most powerful and the only universally admitted cause of bronchial dilatation; second, that all other purported causes are trivial, inconstant, controversial or unsatisfactory in nature; third, that bronchiectasis characteristically has its origin in the pneumonia-producing and thus the atelectasis-producing class of diseases; and last, that atelectasis as above is probably much more frequent as an antecedent of bronchiectasis than its commonly observed frequency indicates; we feel justified in concluding that pulmonary atelectasis furnishes much the most logical and probable explanation of the otherwise obscure and idiopathic cases of pneumonectasis.

### III. CONGENITAL BRONCHIECTASIS

Congenital malformations of pulmonary air chambers (cystic disease) must of course be admitted as possible, but need not concern us here. A dilatation of originally normal sized bronchi in the prenatal nonfunctioning lung does not seem possible in the absence of air entry.

The causes of immediately postnatal ectasia of bronchi may presumably be the same in kind as in acquired bronchiectasis, namely subnormal strength of the bronchial wall, an abnormal intensity of dilating force, or both. Congenital infection (such as syphilis) may conceivably cause weakening of the bronchial wall, as may mechanical tissue faults, and dilatation result from the early normal inspiratory efforts. Such

a process, if it occurs, may correctly be termed congenital bronchiectasis

More within our range of knowledge however are the mechanical dilating stresses. Of the various dilating forces outlined in the initial section of this paper, only two appear to be reasonably probable in the new-born infant, namely atelectasis, and partial bronchial obstruction. Atelectasis we know to be common in the new-born and its dilating value as shown, may be very high. We suggest that failure of the bronchi in congenitally collapsed lung to acquire tonicity incident to function, may well be a contributory cause of dilatation. Partial bronchial obstruction in the new-born, though possible, may be presumed to be much less common than atelectasis. Its dilating effects are as shown, not obvious, but doubtful, and easily to be confused with complete obstruction and atelectasis.

As emphasized for the acquired form of the disease, congenital bronchiectasis when interpreted (3) (6) is much more than mere bronchial dilatation. The radiographic picture is a very conspicuous "whorl" effect in a collapsed lung, indicating gross emphysema, that is, torn lung, or pulmonectasis. Thus the best available explanation of "torn lung" in the very young is that the process is the result of pulmonary atelectasis, congenital or acquired.

A further group is met with in congenital "humpbacks," who not infrequently have pulmonectasis, infected or dry. Here we have an abnormal dilating stress identical in kind with that resulting from atelectasis, namely an over-stretching of the lung to fill a chamber which is too large for it. The kyphosis of elderly people develops so slowly that elastic degeneration keeps pace with the over-stretching of the lung and no high-value pull develops at any time. A purely degenerative type of emphysema rather than bronchiectasis results.

Miller (1) proposes that a failure of the terminal buds to expand into alveoli with the initial inspiratory efforts, transfers the stress to the bronchioles which may consequently dilate. On a physical basis there is no reason why the mechanical pull upon a bronchiole should be increased by the failure of the immediately related potential air sacs to expand. However, if such a process occurs *en masse* we have a material degree of atelectasis, and this as above is an entirely satisfactory explanation of bronchiectasis.

Congenital, like acquired bronchiectasis, appears then in the last analysis to resolve itself largely into a matter of pulmonary atelectasis.

#### IV. THE RÔLE OF INFECTION IN BRONCHIECTASIS

In concluding this analysis of the causes of bronchiectasis, it is necessary to examine the somewhat controversial question as to the relative importance of weakening of the bronchial wall by infection, and of mechanical dilating agents, in the causation of this disease. Many authors both recent and old regard both factors as operative. A further school of thought however proposes that the process is entirely one of destruction, and that it is unnecessary to stipulate mechanical dilating forces. These concepts must be examined in their physical relationships.

##### A. The Replacement Abscess Hypothesis

It is pointed out by Erb (21) and others (25) (26) that complete destruction of the supporting elements of the bronchial wall may occur. Under these circumstances they state that the disease should be regarded as a replacement abscess rather than an ectasia; also that it is not necessary to postulate a physical dilating force. Such a condition is obviously quite possible. In attempting to estimate its probable frequency the following considerations are pertinent.

*The observed pathology:* The severe bronchial destruction recorded by the above authors was observed in rapidly fatal pneumonias in infants. This does not constitute *prima facie* evidence of the characters of the process in those in which a lesser intensity of infection permits survival. Textbooks of pathology describe a wide range of injury to the bronchi up to complete destruction. These sources however frequently record the observation of structurally identifiable bronchial walls and of columnar or ciliated epithelium even in the terminal material upon which they are based, (17) (18) (42) (48) (53) (54) (55) (57) (60) (61). Hyperplastic rather than destructive changes are frequently recorded.

More recently the availability of lobectomy specimens has made possible the study of the anatomical changes in survivors. Under these circumstances the injury is described by Robinson (39) as for the most part an inflammatory reaction in the bronchial wall. Although in the "longer standing" cases varying degrees of injury to the supporting elements of the bronchial wall were seen including complete destruction, it is remarkable that even in this group the epithelium and cilia were for the most part intact. From the standpoint of the present discussion, these observations contain two very significant features. The first is that bronchial dilatation occurred in the inflammatory or predestructive

stage of the infection in those cases in which this stage was observed. Although destructive injury was common in later stages of the disease, it is thus demonstrated that it is possible for this to *follow* rather than *precede* the dilatation. Continued or accelerated injury would in fact be an expected effect of this situation. It follows that destruction of the bronchial walls as seen in late and autopsy material is not satisfactory evidence that this process preceded the dilatation and was a causative agent.

The second significant feature is the frequency with which normal and ciliated epithelium were visualized even where the process was "definitely established." This is of course conclusive evidence that the destructive process in these cases did not pass by continuity of tissue from the lumen to the supporting structures of the bronchial wall. This in turn indicates that bronchiectasis is not necessarily "an excavation in the lung substance starting in a bronchus" as has been stated (25). Neither is the presence of squamous epithelium in itself evidence of destruction and regeneration from residual foci, as metaplastic changes as a result of irritation are characteristic of the bronchial mucous membrane (62).

From the foregoing considerations we must therefore conclude that destruction of the bronchial wall is not shown on a pathological basis to be a necessary forerunner of bronchiectasis. Although the detailed examination of the factors which go to make up bronchial-wall weakening is not within the scope of this paper, these considerations certainly suggest that nutritional, trophic or tonic disturbances may constitute the "weakening" factor before pure destruction can play a part.

*The observed effects of tissue destruction.* The effects of a known complete destruction of a section of lung are common knowledge in the case of tuberculosis and lung abscess. Such known destruction of tissue results in the familiar traumatic artefacts or cavities of these diseases. Because the elastic pull of the lung is exerted in all directions upon the margins of such discontinuous foci, the resulting cavities are, in the closed thorax, uniformly spheroidal in form. If the bronchial wall and surrounding lung are completely destroyed as provided by the replacement abscess hypothesis, the resulting artefacts should at least in some measure approach the anatomical and radiographic characters of those of tuberculous disease and lung abscess, since they are exposed to the same dilating stresses. This is in no way the case. Only rarely is a bronchiectatic cavity spheroidal in form or directly visible in the radiograph.

This dissimilarity in the anatomical characters of the two types of cavities suggests that they are not of common origin, that is, that bronchiectasis is not customarily and basically a destructive lung abscess by nature

*Constant existence of dilating forces* It is important to recognize that even if a mechanical dilating force is deemed unnecessary for the production of bronchiectasis, such forces normal or abnormal are nevertheless constantly present (2). Thus, in the course of a destructive process, a point must be reached at which the existing dilating stress, normal or abnormal, exceeds the tensile strength of the bronchial wall, and ectasia will result. In other words it would seem that the normal elastic pull of the lung must produce ectasia, before a condition of pure replacement abscess could be established, that is, even if destruction precedes the enlargement, the process is nevertheless a mechanical dilatation. Since the bronchi are constantly exposed to dilating stresses whether normal or abnormal in degree (2), the proposal of a purely destructive process without mechanical dilating agents would seem to be untenable.

In the light of the pathological clinical and physical considerations of the preceding three sections we are forced to the conclusion that the replacement-abscess hypothesis does not provide an acceptable explanation of bronchiectatic disease.

### *B Normal Versus Abnormal Dilating Forces*

There remains to consider whether, in the presence of infectious injury to the bronchial wall, dilatation is best explained as being due to the normal elastic pull of the lung as proposed by Warner (2) (5), or whether a dilating stress of abnormal intensity can be customarily expected to be necessary to produce this effect. The former proposal rests upon the undeniable and constant existence of such a normal force, together with the absence of a uniformly identifiable abnormal dilating stress.

Reasons for doubting the efficacy of the normal elastic pull of the lung as a frequent bronchial dilating agent may be expanded as follows

(a) If the normal pull of the lung were a potent factor in the production of bronchial dilatation, this condition would be expected to be a usual or at least a common sequel of pneumonic types of pulmonary infection. This is distinctly not the case.

(b) The elastic pull of the lung in ordinary respiration is a relatively

slight force. Only at the end of a forced full inspiration is it sufficient to produce visible enlargement of the normal bronchi (10). Full inspiration customarily proceeds from cough but even here is not usually the maximum possible inspiration. Even when cough is frequent the duration of this peak force is necessarily an extremely small percentage of the twenty-four hours. Unless the muscular and elastic elements of the bronchial wall have suffered almost complete disintegration there is a tremendous preponderance of time during which they may regain their tone. Again, clinically, cough is apparently an effect rather than a cause of bronchiectasis.

(c) A further weighty argument against the probability of the normal elastic tension of the lung customarily producing bronchial dilatation, is the fact that a large percentage of cases arises during childhood and infancy. At birth however the lung has no elastic tension, and we are told that an average of seven years and a maximum of fourteen years passes before the adult development of the lung is attained (1). This means that the lung has normally an unusually low elastic tension during the very period in which the development of bronchiectasis is common. A causative relationship is therefore not a logical deduction.

(d) The observations of Robinson (39) on lobectomy material show that dilatation regularly precedes destruction of the bronchial wall when the lesion comes under observation at such a stage. The occurrence of dilation at a time when injury to the bronchial wall is of a relatively low order may reasonably be interpreted as indicating that a dilating force of *abnormal* intensity has been operative.

Although this author states, "There was nothing found in our series of cases to indicate that mechanical overstrain such as pleural adhesions, collapsed lung, etc., had played a part," it should be pointed out that this was a highly selected group of cases; that is this group was unusually free from the commonly associated pulmonary infection, otherwise lobectomy would not have been attempted. Thus Smith (43) states, "My experience confirms that of Whittemore that every case of bronchiectasis presents more or less involvement of the parenchyma;" Lord (43, discussion) states, "The pathological process in the lung is ordinarily more important than the bronchial dilatation;" and MacCallum (8) states, "...those acutely produced...are usually associated with lobular pneumonic patches of consolidation." The absence of visible atelectasis, etc., in this series is therefore not a fair indication of the absence of abnormal dilating forces in the average case of bronchiec-



tasis. Again, as formerly pointed out, atelectasis may be dissipated after causing injury.

(c) The high frequency of extensive emphysema in the same section of lung that contains dilated bronchi, as pointed out in a preceding section (II, C), is important evidence that the region has been exposed to an expansile stress of supernormal intensity.

The foregoing pathological clinical and physical considerations then, first, indicate serious doubts that the values of the normal ranges of pulmonary tension are sufficient to frequently produce dilatation of bronchi, and second, that there is important evidence that an abnormal intensity of dilating stress is at least frequently operative. The possibility and probability of bronchiectasis resulting from the normal elastic pull of the lung in the presence of unusual severity of infectious injury should be admitted. The balance of evidence however appears to indicate that the major proportion of cases having infectious injury of average severity are the result of a superimposed dilating stress of abnormal intensity. These considerations are in agreement with the most common trend of thought in the literature that both infectious weakening of the bronchial wall and an abnormal mechanical dilating force are customarily determinative agents in the development of this disease.

#### SUMMARY

1 A detailed examination has been attempted of the nature and value of the various physical forces which are currently held to be causes of acquired bronchiectasis. Correlation has also been made with the recognized clinical and pathological characters of the disease.

2 On these bases it is concluded that the following agents are not shown to exert any clearly significant or frequent dilating stress upon the bronchi. Indeed in some cases they are shown to be constrictive or protective.

- (a) The negative pressure of the pleural space
- (b) Cough
- (c) The pressure of contained secretion
- (d) Partial bronchial obstruction
- (e) The physiological dilatation of the bronchi
- (f) Retraction of scar tissue

3 It is shown that the interpretation of bronchiectasis as being due to some of these causes may result from confusion with the effects of pulmonary atelectasis

4 It is concluded from the physical considerations involved that the concept of bronchiectasis as being due to destruction without mechanical dilating agents is untenable

5 The physical nature of the forces arising as a result of pulmonary atelectasis are, as far as we are aware, for the first time completely described It is shown that the direction, intensity and clinicopathological associations of these forces are such as to provide much the most satisfactory explanation of bronchiectasis, of any of the causes currently proposed It is therefore concluded that atelectasis is probably a causative agent of high frequency in bronchiectasis, and constitutes the most rational explanation as yet available of the otherwise obscure or idiopathic cases of this disease

6 The prevailing opinion that both infectious injury to the bronchial wall and an abnormal intensity of mechanical dilating stress are customarily necessary for the production of bronchial dilatation is corroborated by the detailed examination of the physical principles involved

7 It is pointed out that the bronchiectatic type of disease is not customarily an isolated dilatation of bronchi It is emphasized that the disease is usually characterized by ectasia of both bronchi and respiratory air sacs of common physical origin The term *Pulmonectasis* is therefore recommended as more adequately describing the anatomical situation

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# THE SIZE OF THE HEART IN PULMONARY TUBERCULOSIS

A Report of 400 Cases

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In the minds of many physicians dealing with cardiorespiratory diseases, there appears to be little doubt that in pulmonary tuberculosis the heart is smaller than normal. At least there is a common belief that the cardiac shadow on a teleoroentgenograph taken of an individual with pulmonary tuberculosis is smaller in relation to the transverse diameter of the chest than is found in an individual with no pulmonary disease. This is commonly taught to medical students, and demonstrated in clinics. Certain roentgenologists go so far as to point out cases demonstrating the "drop" heart or "ptotic" heart in the asthenic individual as meaning past, present, or possible future tuberculosis. With these teachings in mind, a search of the literature was made in an effort to determine upon what grounds such assumptions were made, and to ascertain how small a heart must be in relation to the transverse diameter of the chest before it is considered pathological. However, little definite proof was found.

Cardiac measurements were made on 400 cases of pulmonary tuberculosis in an attempt to prove to our own satisfaction that the heart in this disease is smaller than one would normally expect to find in a normal chest of the same size.

## REVIEW OF THE LITERATURE

In spite of the commonly accepted belief that the heart in the phthisical individual is smaller than normal, a review of the literature pertaining to the subject reveals conflicting opinions and relatively scant proof to support some of them. A few take it for granted that not infrequently there is a dilatation and hypertrophy of the right ventricle. Boas and Mann (1), in a paper read before the Section of Medicine of the New York Academy of Medicine, quoted the following men Boh-

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land (a) states that such a hypertrophy is present in chronic tuberculosis and is usually compensatory in nature. Furthermore it is his belief that the enlarged right ventricle, having little reserve, easily becomes insufficient. Krel (b) also mentions that such a hypertrophy is of frequent occurrence. Portal (c), in 1792, on the basis of necropsy studies, believed that the right auricle and ventricle dilate in chronic pulmonary tuberculosis because of obstruction of the pulmonary blood-flow. Laennec, Grissolle, Louis, Rokitansky and Rigal on the other hand state that dilatation of the right heart in tuberculosis occurs only exceptionally. Potain (d) noted that the heart of the phthisical patient was usually small and believed that this was due to the cachexia which accompanied the disease. It was his belief that, in those patients in whom the progress of the disease was very slow, large hearts were often found in which the enlargement was probably due to extrapulmonary causes. Regnault (e) found a true or apparent hypertrophy of the heart in the majority of cases of fibroid phthisis. Dilatation of the right heart, particularly of the right auricle, he claimed could be demonstrated quite frequently among living tuberculosis patients by percussion. Hirsch (f) studied the hearts from 120 necropsies in which he found 35 per cent of the cases showed a marked right ventricular hypertrophy. The degree of hypertrophy paralleled the degree of induration of the lungs and the extent of pleural adhesions. He pointed out the interesting fact that in acute ulcerative tuberculosis the heart was small and atrophied. Wideroe (g) found that right ventricular hypertrophy was quite common in pulmonary tuberculosis and furthermore the greater the age of the individual, and the more extensive the lesion, the more pronounced was the hypertrophy. Bret's (h) findings were similar except that in his series of cases he did not find, in all instances, the degree of parallelism between the types of tuberculosis and cardiac size which was present in the series reported by Hirsch and Wideroe.

Boas and Mann (1) presented data which would tend to disprove the above-mentioned statements. In an electrocardiographic study of 97 patients with pulmonary tuberculosis, it was shown that only 29 per cent displayed right ventricular preponderance, 30 per cent showed left ventricular preponderance, and 41 per cent showed no preponderance of either ventricle. Furthermore, they showed that the right ventricular preponderance is not invariably found in any type of tuberculosis. Left ventricular preponderance is not invariably associated with any particular type of tuberculosis, but was found more commonly among

older patients and twice as frequently in women as in men. Anderson (2), in a study of 100 consecutive admissions to a sanatorium for the treatment of tuberculosis, found that they showed very little deviation from normal, from an electrocardiographic point of view. Neither the degree nor the duration of the pulmonary collapse had any definite relationship to the form of the electrocardiogram. Other studies carried out by Simon and Baum (3) showed that in 250 cases of tuberculosis the electrocardiographic findings varied very little from the accepted normal. In this series 10 per cent of the 250 cases showed a right ventricular preponderance.

Hawes (4) makes the following statement: "Much has been written concerning the small size of the heart in tuberculosis. Some are of the opinion that it is the smallness of the heart, either a congenital or an acquired abnormality, with the consequent poor circulation in the lungs and elsewhere that paves the way for the development of tuberculosis later on." He further states that there are undoubtedly a few individuals of the so-called "Sthenic Habitus," who possess a small heart and in consequence a poor circulatory apparatus. "Such individuals may come down with tuberculosis." Second, he states "in most instances a small heart in tuberculosis is due to the wasting effect on the heart muscle, just as the leg, arm and shoulder muscles waste away from the same cause." Laennec speaks of the small heart in pulmonary tuberculosis. In 1830 Sir James Clark, of London, is quoted by Hawes as stating, "The state of circulation in tuberculosis is subject to great variety. I think the powers of the heart are commonly under ordinary standard, whilst the frequency of pulse is generally above it and palpitation is not an infrequent symptom. A small feeble heart I consider a strong predisposing cause of consumption." Danzer (5) stated that, "When the cardiothoracic ratio is under 45 per cent, it points in favor of tuberculosis in the presence of suspicious lung findings. The lower the percentage, the greater the presumption." Bremer (6) said that a small heart with two large lungs is an important element in the predisposition of phthisis.

Anderson (2) states, "Most students of tuberculosis will agree, I think, with the statement that there are no definite cardiac signs accompanying the majority of tuberculous cases and that the disease has no specific effect on the heart aside from that produced by any chronic, debilitating malady."

## THE SIZE AND SHAPE OF THE HEART

It is a well known fact that the shape of the heart depends to a large degree upon the shape and size of the body frame. In the asthenic individual, the thorax is long and flat and in this type of chest one commonly finds the so called "drop" heart, or Kraus and Wenckebach's *Cor pendulum*. The smallness of the heart in this type of chest may be more apparent than real. This is equally true in the hypersthenic type of chest in which we find the diaphragm pushing the apex of the heart upward and tilting the entire heart in such a manner as to give one the impression of cardiac enlargement. This enlargement is also more apparent than real.

There are other factors which enter into the problem of determining cardiac size and shape. Holmes and Ruggles point out in their textbook of roentengenology that age, height, weight, and sex influence the size and shape of the cardiac shadow. Keeping this in mind one realizes that it is practically impossible for the clinician or roentgenologist to determine whether a heart is "slightly small" or "slightly large" simply from a teleoroentgenogram. Some of the methods that have been suggested as a means of simplifying the problem will be mentioned.

Moritz, in 1902, proposed a complicated system of vertical, longitudinal and transverse diameter measurements in an effort to determine the normal relationship between the diameter of the heart and the diameter of the chest. Other investigators who have contributed to the literature on this subject are Clayton and Merrill (7), Williamson (8), Shattuck (10), Bardeen (9), B. Smith (11), H. E. Smith and Bloedern (12), Danzer (5), Eyster (13), Hodges and Eyster (14), Banton (15), and probably many others. No time will be spent in discussing the different methods proposed by these men. The method proposed by Hodges and Eyster was the one used in the study of this series.

## METHODS

We realize that the formula recommended by these authors was to be used primarily when orthodiagraphic technique was employed for determining the transverse diameter of the heart. We believe that this will detract in part from the value of the paper but we also believe that mathematically the error is too small to be of great importance.

The formula for determining the transverse diameter of the heart is as follows:  $TD = 0.1094 \times A - 0.1941 \times H + 0.8179 \times$



W-95 8625, when TD = transverse diameter (in mm), A = age (in years), H = height (in inches) and W = weight (in pounds) This formula was suggested after a study of 80 subjects had been made in which there was no evidence of cardiac pathology A later article by Eyster (13), in which another 100 patients were added to the original, showed that 3 per cent exceeded the predicted transverse diameter by more than 10 per cent, which means that it is 19 per cent more efficient than assuming an average for all cases

In their original article the authors pointed out that, of the variables, weight exerted the greatest effect on the transverse diameter Age was next in importance and height affects the transverse diameter least

TABLE 1

*A tabulated summary showing age distribution and a comparison of the measured transverse diameter (MTD) and the predicted transverse diameter (PTD) of the different age groups*

AGE	NUMBER OF CASES	PER CENT	MTD > PTD		MTD < PTD		MTD = PTD	
			Number	Per cent	Number	Per cent	Number	Per cent
<i>years</i>								
18-20	6	1.5	4	66.6	2	33.3		
20-30	176	44	85	48.4	76	43.1	15	8.5
30-40	142	35.3	78	54.6	24	37.8	10	7.7
40-50	50	12.5	26	52	21	42	3	6
50-60	25	6.25	10	40	11	44	4	16
60-67	1	.25						
All ages	400		203	50.5	165	41.5	32	8

## DATA

The present report is the result of a study made of the teleoroentgenograms of 400 patients who had pulmonary tuberculosis Of this number 54, or 13.5 per cent, are dead Of the remaining 346, some are still in the hospital under treatment, some were discharged as apparently arrested, while others left the hospital against medical advice Therefore it is quite possible that more than 54 are now dead but we have no record to show this to be true

All of the patients were male beneficiaries of the United States Marine Hospital, and had been sent to Fort Stanton for the treatment of pulmonary tuberculosis The age range was from 18 to 67 years, and age distribution was as follows from eighteen to twenty, 6 (1.5 per cent), twenty to thirty, 176 (44 per cent), thirty to forty, 142 (35.5 per cent),

forty to fifty, 50 (12.5 per cent), fifty to sixty, 25 (6.25 per cent), sixty to sixty-seven, 1 (2.5 per cent)

Essentially all types of pulmonary tuberculosis were represented in this group

The transverse diameter was measured from the original X-ray film in practically all instances. The predicted diameter was computed on

TABLE 2

*A summary showing the age distribution of the deaths and a comparison of the measured transverse diameter (MTD) and the predicted transverse diameter (PTD) of the different age groups*

AGE	NUMBER OF DEATHS	PER CENT	MTD > PTD		MTD < PTD		MTD = PTD	
			Number	Per cent	Number	Per cent	Number	Per cent
<i>years</i>								
20-30	30	55.5	14	46.6	12	40	4	13.3
30-40	13	24	9	69.2	3	23	1	7.7
40-50	8	14	3	37.5	5	62.5		
50-60	3	5	1	33.3	1	33.3	1	33.3
All ages	54		25	46.29	23	42.59	6	11.12

TABLE 3

*A group summary of the average age, height, admission weight, normal weight, measured transverse diameter, predicted transverse diameter and predicted transverse diameter on the basis of the normal weight of the various age groups*

AGE	AVERAGE AGE	AVERAGE HEIGHT	AVERAGE ADMISSION WEIGHT	AVERAGE WEIGHT NORMAL	AVERAGE MTD	AVERAGE PTD	PTD ON BASIS OF NORMAL WEIGHT
<i>years</i>	<i>years</i>	<i>inches</i>	<i>pounds</i>		<i>mm</i>	<i>mm</i>	
18-20	18.66	69.3	139	146	115	112.4	117.9
20-30	24.4	68.6	141.8	150	116.3	116.7	120.9
30-40	34	68.8	144	155	121.5	118.99	125
40-50	44.3	68.8	144	154	121.6	120	123.4
50-60	55.4	70	143	156	117.9	118.6	124
60-67	67	66	141	160	120	122	122

the basis of admission age, admission weight, and admission height. The normal weight of the patient was also recorded on his admission to the hospital. Therefore the measured cardiac diameter at the time of entrance to the hospital was compared with the predicted diameter using both the admission weight and the patient's normal weight.

After the computation had been made, the cases were grouped according to age, and a survey was made to determine in how many instances

the heart was smaller than the predicted normal, larger than the predicted normal or the same as the predicted normal The results are shown in table 1

The deaths were separated from the entire group and a similar tabulation was made (table 2)

A grand average for age, height, admission weight, normal weight, and predicted diameter of the different age groups is recorded in table 3

#### REMARKS

In this study, as is often the case in clinical investigation, our aim was to establish proof to a belief, namely that the heart of the individual having pulmonary tuberculosis is smaller than the predicted normal on the basis of weight, height and age We found, however, that this was not true of this group of four hundred We do not wish to draw conclusions from our study We are merely summarizing our findings Whether or not the altitude of the hospital, which is 6000 feet above sea level, has any influence on the size of the cardiac shadow is a matter for speculation

#### SUMMARY

1 A study was made of the teleoroentgenograms of 400 patients having pulmonary tuberculosis

2 Their ages range from 18 to 67 years

3 The study included all clinical types of pulmonary tuberculosis

4 A comparison was made between the measured transverse diameter of the heart and the predicted transverse diameter

5 Of the 400 cases, 203 (50.5 per cent) had a measured transverse diameter greater than the predicted diameter, 165 (41.5 per cent) had a measured transverse diameter of less than the predicted diameter and 32 (8 per cent) had a measured transverse diameter equal to the predicted diameter

6 As is shown in table 2, in a study of the X-ray films of the 54 cases that died, there was very little difference noticed as compared with the general average

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## TUBERCULIN ALLERGY PRODUCED BY PARENTERAL BCG VACCINATION<sup>1 2</sup>

CAMILLE KERESZTURI, HAROLD A ROSENBERG AND WILLIAM H PARK

This report of the development of allergy to Old Tuberculin following parenteral BCG vaccination is based upon the study of 41 subcutaneously and 292 intracutaneously vaccinated children. Since different interpretations in reading tuberculin tests are probably responsible for the wide variations reported in the literature on the subject, a definition of our standards is given.

All tests are done by the Mantoux method of intracutaneous injection. The minimum reaction considered positive is one in which the induration is at least 10 mm in diameter. All reactions smaller than this, and reactions in which erythema alone is present, are called negative. The routine doses of Old Tuberculin on which this study is based are 0.1 and 0.2 mgm. Positive reactions to smaller doses, and negative reactions to larger doses are also considered in our tables. With these doses most reactions measure 10 to 30 mm in diameter. Occasionally we encounter larger reactions or blistering. Sometimes we use larger doses, ranging from 1 to 100 mgm Old Tuberculin in testing suspicious reactors. Positive reactions to these large doses of Old Tuberculin are not included in the present tables.

A comparison of allergy following intracutaneous and subcutaneous vaccination is not quite justifiable because of the different doses of vaccine used in the two groups. The use of smaller doses of vaccine for subcutaneous vaccination is essential in order to reduce the number of cold abscesses at the site of inoculation. However, even if dissimilar doses of vaccine were used for the subcutaneous and intracutaneous BCG vaccination, a comparative study is important in evaluating the efficacy of the two methods in producing allergy.

<sup>1</sup> From the Department of Health, New York City.

<sup>2</sup> This study is based on material collected in connection with the BCG investigation by the pediatric staff of the Bureau of Laboratories, New York City. The staff consisted of Dr C Kereszturi, Dr M I Levine, Dr P Vogel and Dr H Rosenberg, pediatricians, Margaret F Sackett, R N, Rayne P Stebbins, R N, and Gertrude Richardson, R N, visiting nurses, Agnes Leach, social worker.

From chart 1 it is seen that allergy develops sooner and in relatively more cases in the intracutaneous group than in the subcutaneous group. The chart is self-explanatory.

In the intracutaneous group, 53 cases have been tuberculin tested weekly following vaccination. At the end of the first week following

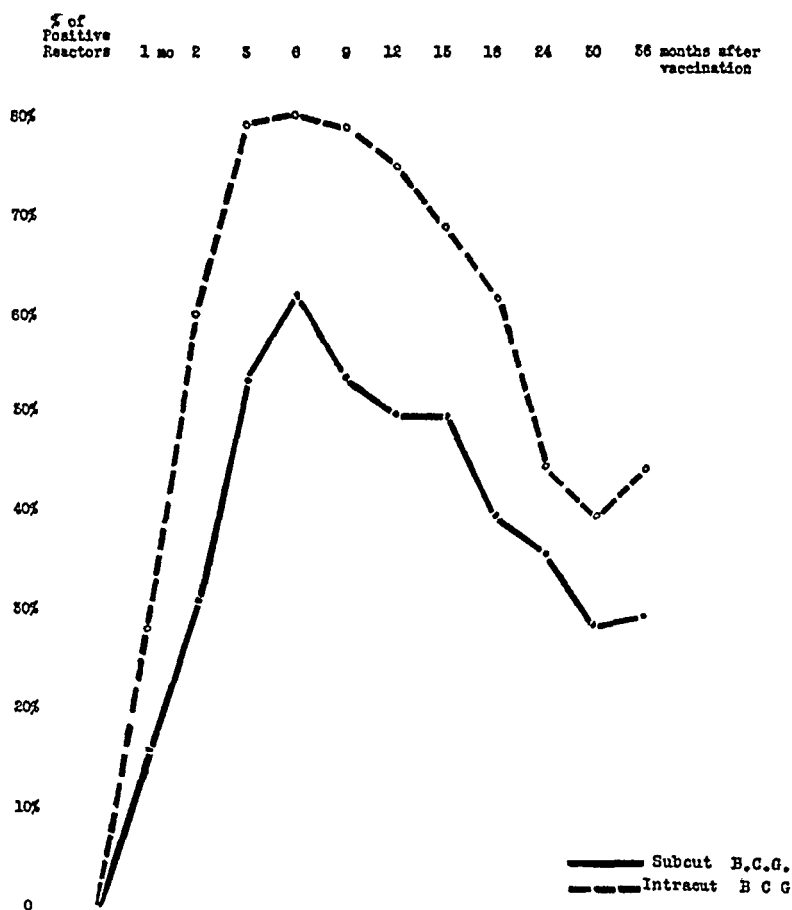


CHART 1 The development of allergy to Old Tuberculin following subcutaneous and intracutaneous BCG vaccination

vaccination, none of the cases have become allergic. At the end of the second week, two cases (4 per cent) reacted positively, at the end of the third week, 8 (15 per cent) and at the end of the fourth week, 15 (28 per cent).

As was previously stated, this report is limited to a study of allergy to

doses of 0.1 and 0.2 mgm of Old Tuberculin Wallgren (1), in a study of 33 intracutaneously vaccinated children, found they all developed a positive Mantoux reaction to 1.0 mgm. He reports that hypersensitivity usually develops in six to seven weeks, and always by the sixteenth week. He advises revaccination if allergy fails to develop by the sixth or seventh week. Parisot and Saleur (2), reporting on 651 infants subcutaneously vaccinated with 0.01 to 0.02 mgm of BCG, found but 62 per cent positive Mantoux reactions in the group. The dose of Old Tuberculin used is not stated. In 914 subcutaneously vaccinated newborn infants who were given a dose of vaccine comparable to 0.01 of our vaccine, (400,000 bacilli), Cantonnet (3) reported 54 per cent positive Mantoux reactions in one year. Foley and others (4) found 48 per cent of 285 subcutaneously vaccinated children had developed a positive Pirquet. At the seventeenth month following vaccination, the number of positive reactors was reduced to 18 per cent. In a study of a group of parenterally vaccinated children, Domenech (5) found that one-third of the cases became Pirquet positive after vaccination. However, when the group was Mantoux tested with 10 mgm of Old Tuberculin, every case gave a positive reaction. It has been our experience that the use of doses of tuberculin ranging from 1.0 to 10.0 mgm for testing increased the number of positive reactions only 10 per cent.

The development of allergy following intracutaneous and subcutaneous BCG vaccination has been studied in relation to the following factors

- (1) Dose of vaccine
- (2) Age of vaccine
- (3) Age of patient at time of vaccination
- (4) Local lesion
- (5) Lymph node reaction
- (6) Exposure before and after vaccination

The number of cases in the subcutaneous group is very small and therefore the figures of that group will be presented occasionally without comment. However, sufficient cases are available in the intracutaneous group to warrant studying the effect of the factors mentioned above upon the development of allergy.

(1) *Dose of vaccine* As we have previously stated, smaller doses of vaccine are used for subcutaneous than for intracutaneous vaccination. The doses range in the former from 0.01 to 0.5 mgm, in the latter, from

0.03 to 0.30 mgm On several occasions, the dose was divided, and equal parts given in each thigh, represented in table 1 as  $2 \times 0.15$  and  $2 \times 0.01$  One milligram of the bacterial suspension contains 40 million slightly virulent bacilli

It would appear from these findings in table 1 that a dose of 0.15 mgm is superior to smaller doses in producing allergy, but larger doses do not increase this advantage In the small subcutaneous group, the 0.01 dose is superior to smaller doses in producing allergy Both patients who received larger single doses, 0.03 and 0.05 mgm, developed a positive

TABLE 1

*Comparative study of allergy in subcutaneous and intracutaneous BCG vaccination in relation to dose of vaccine*

DOSE	NUMBER OF CASES	POSITIVE MANTOUX REACTION
Intracutaneous vaccination		
mgm		
0.003 to 0.1	33	18 (55%)
0.15	169	142 (84%)
$2 \times 0.15$	24	21 (87%)
0.30	21	16 (76%)
Subcutaneous vaccination		
0.001 to 0.005	21	10 (48%)
0.01	6	5 (83%)
$2 \times 0.01$	5	4 (80%)
0.03		
0.05	2	2 (100%)

Mantoux reaction However, with these larger doses, the incidence of local cold abscesses is high and therefore they are undesirable

(2) *Age of vaccine* The bacillary suspension used for vaccination in this study is prepared from culture every ten days The age of the vaccine consequently ranges from one to ten days From table 2 it is apparent that the older vaccine is as efficacious in producing allergy as that freshly prepared The age range of the vaccine is small, and it is problematical whether any difference would be found with vaccines several weeks old In this respect, Heimbeck (6) found that ten cases who were given 45-day-old vaccine subcutaneously all failed to develop a positive Pirquet reaction



(3) *Age of patient at time of vaccination* In a group of 251 intracutaneously vaccinated children whose allergy was studied in reference to their age, 238 (95 per cent) were less than one year of age. No difference in the frequency of positive reactors during any period of the first year was

TABLE 2

*Comparative study of allergy in intracutaneous BCG vaccination in relation to age of vaccinee*

AGE	INTRACUTANEOUS	
	Number of cases	Positive Mantoux reaction
<i>days</i>		
0-2	42	36 (85%)
2-4	45	37 (82%)
4-6	62	53 (85%)
6-8	42	31 (74%)
8-10	51	42 (82%)

TABLE 3

*Comparative study of allergy in intracutaneous and subcutaneous BCG vaccination in relation to age of patient*

AGE	NUMBER OF CASES	POSITIVE MANTOUX REACTION
Intracutaneous vaccination		
<i>months</i>		
0-6	184	150 (82%)
6-12	54	48 (88%)
12-36	13	4 (31%)
Subcutaneous vaccination		
0-6	16	8 (50%)
6-12	11	7 (64%)
12-72	14	8 (57%)

noted (table 3). The age is represented in table 3 in six months periods. However, a more detailed study was also done, considering the age of the children when vaccinated, at monthly intervals, but no difference was found. Only 13 children vaccinated after the first year of life are available for this study, 4 of whom became allergic. We do not feel justified in drawing any conclusions from this small number. In the subcutaneous group, no difference in the frequency of the development of a positive Mantoux reaction was noted at different ages.

(4) *Local lesions* Local lesions which develop following vaccination with BCG differ according to the method of injection of the vaccine. Following intracutaneous vaccination, a lesion resembling a solitary maculopapular tuberculide developed in 91 per cent of the cases, and became necrotic in 53 per cent. In the subcutaneous group, a deep nodular mass was felt in 61 per cent. The mass enlarged and broke through the skin in 54 per cent.

We may conclude from the data in table 4 that the development of allergy bears a direct relationship to the severity of the local reaction to the vaccine. This is in accord with the report of Foley and others (4). In a group of 285 subcutaneously vaccinated children, they found a

TABLE 4

*Comparative study of allergy in intracutaneous and subcutaneous BCG vaccination in relation to local lesions*

LOCAL LESION	NUMBER OF CASES	POSITIVE MANTOUX REACTION
Intracutaneous vaccination		
No local lesion	26	11 (42%)
Local lesion—not necrotic	138	107 (78%)
Necrotic local lesion	119	105 (88%)
Subcutaneous vaccination		
No local lesion	16	6 (37%)
Nodular mass—no ulceration	3	1 (33%)
Cold abscess—ulceration	22	17 (77%)

positive Pirquet reaction in 48 per cent. However, among 22 of the group with local nodules, and in 68 who developed cold abscesses, the incidence of a positive Pirquet reaction was 90 per cent.

(5) *Inguinal lymph node reactions* Following vaccination on the thigh, enlargement of the inguinal lymph nodes was evident to clinical examination in 76 per cent of the intracutaneous and 56 per cent of the subcutaneous cases. The nodes suppurated in 15 per cent of the intracutaneous group, and in 2 per cent of the subcutaneous cases. A survey made recently in our group has revealed that the number of suppurating inguinal nodes following intracutaneous vaccination with 0.15 mgm BCG is over 25 per cent. The relationship between the development of

allergy and enlargement and suppuration of the inguinal nodes is presented in table 5

The data in table 5 show very strikingly that, as was noted in the study of local reactions, there is a direct relationship between the severity of the lymph node reaction and the development of allergy

TABLE 5

*Comparative study of allergy in intracutaneous and subcutaneous BCG vaccination in relation to demonstrable alterations in inguinal lymph nodes*

LYMPH NODES	INTRACUTANEOUS		SUBCUTANEOUS	
	Number of cases	Positive Mantoux reaction	Number of cases	Positive Mantoux reaction
No nodes	67	37 (55%)	19	8 (42%)
Enlarged nodes	173	143 (83%)	21	13 (62%)
Suppurating nodes	43	43 (100%)	1	1 (100%)

TABLE 6

*Comparative study of allergy in intracutaneous and subcutaneous BCG vaccination in relation to exposure*

EXPOSURE	INTRACUTANEOUS		SUBCUTANEOUS	
	Number of cases	Positive Mantoux reaction	Number of cases	Positive Mantoux reaction
Exposure within three months prior to vaccination				
No exposure	89	62 (70%)	21	7 (33%)
Exposure to closed tuberculosis case	68	60 (88%)	5	4 (80%)
Exposure to open tuberculosis case	91	77 (85%)	15	12 (80%)
Exposure after vaccination				
No exposure	121	88 (73%)	30	16 (53%)
Exposure to closed tuberculosis case	73	58 (79%)	5	2 (40%)
Exposure to open tuberculosis case	57	50 (88%)	6	5 (83%)

(6) *Exposure to tuberculosis* We have divided our study of allergy in relation to exposure into two phases (1) exposure to tuberculosis occurring within three months prior to vaccination, and (2) exposure occurring immediately after vaccination. Since only those children with a negative tuberculin reaction are eligible for vaccination, exposure longer than three months prior to vaccination should theoretically have no effect upon the development of allergy following vaccination.

From table 6, we see that a higher percentage of those children who were exposed to open tuberculosis within three months prior to vaccination developed a positive Mantoux reaction than children not exposed. There are several possible explanations for this unexpected finding. It may be a purely accidental finding, or a number of the children who were exposed to open tuberculosis, and gave a negative tuberculin reaction at the time of vaccination, may have already been naturally infected, and been in the preallergic incubation period of tuberculosis, or many of the children exposed to open tuberculosis before vaccination continued to be exposed after vaccination as well. The greater incidence of allergy in the exposed group may very well be due to the subsequent exposure rather than that which preceded the vaccination.

We would naturally expect exposure following vaccination to affect the incidence of the development of allergy, since some of the children exposed to open tuberculosis may become naturally infected. Aronson and Dannenberg (7), in a study of 70 orally vaccinated infants, found no definite relationship between the incidence of allergy and the type of exposure following vaccination. They report positive tuberculin reactions in 82 per cent of the cases exposed to open tuberculosis, in 93 per cent exposed to closed tuberculosis, and in 75 per cent who were not exposed. Turpin (8), however, found 10 to 20 per cent more positive reactors in a group of orally and parenterally vaccinated children who lived in a tuberculous environment as compared to a vaccinated group in a nontuberculous environment.

The positive tuberculin test produced by BCG vaccination is not a permanent phenomenon. In a considerable percentage of the cases the tuberculin allergy becomes less intensive between six and twelve months after vaccination and gradually becomes negative after twelve months.

The relative number of disappearing positive Mantoux tests in the exposed group is less than in the nonexposed. At the end of thirty months, there are 64 per cent positive reactors in the former group as compared to 40 per cent in the latter. This is probably attributable to the occasional occurrence of natural infection in the exposed group.

All findings thus far reported have comprised results following one vaccination only. Children who were revaccinated were scored only to the time of the second vaccination. In the small group of children who were vaccinated more than once, an interesting finding was noted

This group comprises only children who failed to develop allergy following the first vaccination

The findings presented in table 7 indicate that there are apparently some children who cannot be made allergic to Old Tuberculin despite repeated vaccinations with BCG. A satisfactory explanation of this phenomenon cannot be offered.

TABLE 7

*Study of allergy following revaccination with BCG in children who did not develop allergy following the first vaccination*

METHOD	FOLLOWING 1ST REVACCINATION		FOLLOWING 2ND REVACCINATION		FOLLOWING 3RD REVACCINATION		FOLLOWING 4TH REVACCINATION	
	Num ber of cases	Positive Mantoux reaction	Num ber of cases	Positive Mantoux reaction	Num ber of cases	Positive Mantoux reaction	Num ber of cases	Positive Mantoux reaction
Intracutaneous	26	11 (42%)	10	1 (10%)	2	0 (0%)	1	0 (0%)
Subcutaneous	13	3 (23%)	7	1 (14%)		(0%)		(0%)

## SUMMARY

1 A report of the development of allergy to Old Tuberculin (0.1 and 0.2 mgm) in 292 intracutaneously and 41 subcutaneously vaccinated children is presented.

2 Relatively more of the intracutaneous group developed a positive Mantoux reaction than of the subcutaneous group, 80 per cent and 62 per cent respectively.

3 Allergy developed sooner in the intracutaneous than in the subcutaneous cases. The highest incidence of allergy in both groups occurred at the end of the sixth month.

4 The percentage of positive Mantoux reactors at the end of the first year following vaccination was 75 per cent in the intracutaneous group, and 50 per cent in the subcutaneous group, at the end of the second year, 45 per cent and 36 per cent, at the end of the third year, 42 per cent and 30 per cent.

5 In the intracutaneous group, a 0.15 mgm dose produced a greater incidence of allergy than smaller doses. Larger doses showed no advantage over the 0.15 mgm dose. In a small dose range used for subcutaneous vaccination, no effect upon the incidence of allergy was noted. Two cases with 0.05 mgm doses both developed a positive Mantoux reaction, but such doses have the undesirable feature of producing local cold abscesses.

6 The incidence of the development of allergy was not influenced by the age of the patient at the time of vaccination

7 A direct relationship exists between the incidence of the development of allergy and the severity of the local reaction

8 A direct relationship exists between the incidence of the development and the severity of the reaction of the regional lymph nodes

9 The age of the vaccine (1-10 days) does not influence the incidence of positive Mantoux reactors

10 Relatively more cases exposed to open tuberculosis before vaccination became positive to the Mantoux test than those not exposed

11 Relatively more cases exposed to open tuberculosis after vaccination became Mantoux positive than those not exposed

12 There were some children who could not be made allergic to Old Tuberculin despite several vaccinations with BCG

#### CONCLUSIONS

1 From the point of view of production of allergy to Old Tuberculin the intracutaneous BCG vaccination is superior to the subcutaneous method

2 The optimum dose of vaccine for producing allergy in the intracutaneous group is 0.15 mgm

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## TREATMENT OF PULMONARY TUBERCULOSIS WITH GOLD SODIUM THIOSULPHATE<sup>1, 2</sup>

MELVIN TESS

During the past twelve years since Møllgaard (1) published the results of his study of sanocrysin (gold-sodium-thiosulphate) and made claims that the substance has a specifically curative effect in tuberculosis, there have been hundreds of men who have tried the drug on patients and reported their results. However, there is still no uniform opinion as to its place as a therapeutic agent. Most of the writers in foreign countries, but not all by any means, report good results and advocate its continued use, some advocating it along with other treatment, while others rely upon it solely, combined with bed-rest. The writer received the impression that in the United States the predominant opinion is that gold is of little or no use (2) (3). Since there are many who have derived unquestionably good results and since we cannot accurately compare clinical records and statistics of any two writers, because each has his individual method of interpreting results, it appears that work with sanocrysin will continue for some time before universal agreement as to its merits can be determined.

An exhaustive review of the literature for this type of a report is obviously unnecessary. However, it was thought practical to mention some of the fundamental facts that have been observed by others and have been the grounds for much discussion.

Møllgaard believed that sanocrysin, introduced into the bloodstream, permeates tuberculous lesions and there kills many, if not all, offending bacilli. The resulting reactions were interpreted as being due to the liberation of toxins from the bacilli, that is, a tuberculin-like reaction. To offset these reactions, he prepared and administered, at the first sign of a reaction, an antiserum obtained from horses which had been injected with "defatted" formalin-treated bacilli. Some men insist that this antiserum must be given, and that the cause of so many unfavorable

<sup>1</sup> From the Robert Koch Hospital, St. Louis Municipal Tuberculosis Sanitarium, Koch, Missouri.

<sup>2</sup> Read before the Trudeau Club of St. Louis, St. Louis, Missouri, May 7, 1936.

results is due to the fact that many men failed to accept Møllgaard's advice that this serum be used. The general opinion now held is that most of the reactions are symptoms of metallic poisoning and not tuberculin-like shock. Therefore, the serum has been discarded by most clinicians and recourse has been made to smaller and less frequent doses of gold.

According to the present-day opinion, the action of sanocrysin is due to stimulation of the natural defences of the body, producing increased resistance and a stimulating effect on the formation of new connective tissue (4) (5), and not a bactericidal action as Møllgaard proposed. The increased resistance manifests itself by lowered temperature, gain in weight, more favorable blood counts and disappearance of tubercle bacilli from the sputum. The formation of connective tissue is apparently due to stimulation of the reticuloendothelial system and fibrogenetic tissue (6). The contraction of this connective tissue causes the pulling together of cavities and a tendency to fibrosis as shown by X-ray.

Since the action of sanocrysin is one of healing and stimulation of cells entering into the formation of scar tissue, it is quite obvious that when such tissue has already been formed, as in old fibroid cases, little good can be expected. Early cases, those of not more than a year's duration, seem to show the best results. By early cases I am not referring necessarily to those with little involvement, as the Minimal or Moderately Advanced group, but only to those with short duration of the disease. Such early cases that are of the acute or subacute type, or chronic fibrocascous types in which there are relatively recent discrete tubercles, are the cases that are most often favorably affected. (We did not take this into consideration in the selection of our group as I shall describe later.)

Another large group of patients to whom gold is often given with favorable results, are those in whom collapse measures are used. Cases having pneumothorax, phrenic nerve operations, or thoracoplasties, in whom there occurs a spread of the disease to the better side, often have the new process controlled by gold therapy.

The early workers used large single doses and continued them until a large amount of gold had been given. It was thought by many that a reaction must be produced in the patient in order to get results. It was not uncommon to begin with doses of 500 mgm and rapidly increase them to 1000 or even 1500 mgm. The total dosage varied between 10 and 30 grams. It did not take long, however, for men to observe that the patients could not tolerate this. Most men now begin with 50 to 100



mgm and gradually increase to a maximum single dose between 500 and 750 mgm. The sum of all the gold given varies between 6 and 9 grams.

Some of the results often observed are a drop in temperature, rather gradual (over several months duration), and often to normal. This, of course, is absent in a chronic group of patients (such as ours was) because the temperature usually approaches normal. If the dosage is not too large and no gastrointestinal involvement exists, the appetite is often stimulated and the patient gains weight.

As the lesion in the lung forms scar tissue, the sputum decreases markedly in amount. Various writers report the disappearance of tubercle bacilli from the sputum in as high as 50 to 75 per cent.

The blood examination done by many shows a return of the sedimentation rate to normal and a differential count that approaches normal. A substantial increase in monocytes is observed by some men, being interpreted as a stimulation of the reticuloendothelial system (4) (6).

The subjective feeling of well-being is also described by many. It is only natural to expect such an occurrence with the disappearance of toxicity.

The complications encountered are chiefly those of heavy-metal poisoning. Nausea and vomiting are about as frequent as seen in cases receiving salvarsan. The severity and duration varies with the individual. A certain number cannot tolerate gold at all and in them the injections must be decreased or stopped entirely. One must be careful to give the gold on an empty stomach and caution the patient to eat lightly at the following meal. Along with these complaints occur chilly sensations and rise in temperature. Such symptoms rarely persist over twelve to twenty-four hours. Albuminuria of moderate degree may be observed frequently. Treatment need not be stopped for this, but large amounts of albumin require immediate discontinuation of gold. Skin eruptions, usually of a mild degree, occur in individuals sensitive to gold. These may go on to an exfoliative dermatitis and death. It is well to discontinue gold in the presence of a dermatitis, at least for a time, and if return to gold is advisable, do so cautiously with small doses. Icterus caused by liver damage is a rarer complication and accompanied by death in many cases. Stomatitis with ulcerative lesions and salivation may be encountered. Aching in the limbs and joints, usually transient, occurs at times. In fact, all complications seen from heavy metals may be manifested by gold.

An excitation of the lesion with a definite spread by X-ray and physical

examination, high temperature, and general toxicity may be seen. Such cases usually occur in patients receiving large doses.

One cannot tell by any previous symptoms or by any type of lesion present, the group of cases that will react unfavorably. Aside from the group who are extremely ill (who should, of course, be excluded), one may expect complications in any of the patients. It is for this reason that treatment must be started with small doses, and increased according to the patient's tolerance. Some will be found who will not tolerate gold at all.

#### OUR APPROACH

Since no previous work with gold had been done at Koch Hospital, and since excellent laboratory and X-ray facilities were available, we decided to observe the action of this drug on a number of our patients. Arrangements were made with the Abbott Laboratories, and they generously furnished without cost enough gold-sodium-thiosulphate to carry out our experiment. (Sanocrysin is the trade name given the substance by the original manufacturers. Therefore, we rightly should refer throughout to our substance as gold-sodium-thiosulphate, which is the correct chemical name of the drug, however, since many know this drug better by the term "sanocrysin," we shall often refer to it by this name, or simply "gold.")

At the start of the course of treatment, the entire staff and I myself were more or less prejudiced against gold. If one reviews the literature critically this is only to be expected. With this fact in mind, our series would of necessity comprise those patients in whom the staff considered collapse therapy inadvisable, and those in whom the past treatment had been inadequate to control the disease. All patients had had the disease (with two exceptions) for over one year (some had had it fifteen years). All cases showed bilateral involvement, many with extensive infiltrations and cavitation. The actual average duration of disease of all patients was five and one-half years. I mention this to show that the group chosen was far from ideal, it was not at all the type in which gold was indicated, as recommended by other men, and it was, in fact, a group in which nothing but sanatorium routine could be offered.

Fifty odd cases of this type were selected throughout the hospital and presented at staff meetings. Those in whom some type of collapse measure seemed indicated were withdrawn, leaving forty-eight in all.

Recognizing the necessity of controls, the group was divided approxi-

mately in half To make an unbiased control of an experiment with tuberculous patients is a most difficult task However, we followed closely along the method advocated by Sweany (4) for his group of patients We used the following four methods of control

- (1) A group of patients as nearly like the treated patients as possible, selected with the help of the residents on whose divisions the patients were The residents and myself reviewed the X-rays, physical examinations, laboratory reports, temperature curves, and in this manner got two groups as comparable as possible A half-dozen, rather than one man's judgment, made the selection
- (2) Any patient with tuberculosis is apt to do better if he feels that something is being done for him Therefore, the control group received saline intravenously every time the other group received gold Six of the control group were told that they received gold along with their antisyphilitic treatment All who consented received at least some form of injection
- (3) One patient who was selected for treatment refused and was added to the control group
- (4) "Auto-control" By this we mean a comparison of the patient's clinical course before and following treatment This, of course, supplies the most valuable means of control

At the end of the course of treatment the patient's X-rays, physical examinations, laboratory reports, temperature, etc were again reviewed by the various resident physicians, the roentgenologist, and myself After due consideration of all these factors the patients were classified as to whether they were improved, unchanged, or worse

If all the cases selected had been in good condition we would have expected good results with or without gold However, since all the patients were in rather poor condition, we should not attribute a change for the worse entirely to gold if the control group also showed such a change Therefore, the comparative results, six months after the beginning of the treatment, in the treated and control groups are the basis for commending or condemning gold therapy

The course of treatment was begun with 5 mgm, then 10, 25, 50, 100, 250, and on up Two single injections of 500 mgm were given Most of the men who stood the treatment well received about 400 mgm per dose The women received usually between 250 and 333 mgm This was continued so that the total dosage for men was set at 6,000 mgm and for women between 4,000 and 5,000 mgm Some patients had complications and only small doses could be given, while in others

treatment had to be stopped When smaller doses were used, that is, up to a dose of 100 mgm, injections were given two to three times a week With larger doses the interval was increased to one week or ten days

In view of my sceptical attitude at the beginning of this study I was surprised at the wholly unexpected benefit derived from the treatment

In estimating the clinical course due consideration was given to subjective symptoms, temperature, weight, physical signs, roentgenological findings, sputum and blood counts Table 1 summarizes the clinical course of the entire series

Three in each group died However, the deaths in the gold group could not be definitely ascribed to the treatment The first man who died had received only 50 mgm in four divided doses This total amount is much less than many workers have given for the first injection

TABLE 1  
*Summary of the results in the treated and control groups*

	GOLD GROUP	CONTROL GROUP
Number	26	22
Slightly improved	6	2
Definitely improved	9	2
Unchanged	2	7
Slightly worse	4	2
Much worse	2	6
Dead	3	3
Slight toxic effects	4	
Severe toxic effects	4	

He had a large haemorrhage and died several days later The second man had received only 225 mgm in seven divided doses This total amount likewise is less than some authors recommend for the initial dose and it would seem to be too small for a lethal toxic effect This patient, too, haemorrhaged and died in about one week The third patient, a white female, had received 1,325 mgm Her treatments had been discontinued two weeks before her death because she had complained of an aggravation of gastrointestinal distress, which had been present previously She likewise had a haemorrhage and died two days later With her haemorrhage she had severe pain in the left chest and became dyspnoeic It was suspected that she developed either a spontaneous pneumothorax or an atelectasis due to the plugging of a bronchus with blood Preceding the haemoptysis, this patient had been in a fair

general condition These three fatal cases had marked bilateral disease with large bilateral cavities

Our percentage of benefited patients compared very favorably with those of other groups as listed by Sweany (4), especially when we consider the advanced stage of the disease and the poor results of the control series

The average age of the gold group was 38 years and of the control group 40 years The average duration of illness for the gold group was 5.7 years, and for the control group 5.4 years For those definitely improved the average duration of illness was between 3 and 3½ years, substantiating what has been said before, that earlier cases receive the most benefit from this form of treatment

TABLE 2  
*Results according to color and sex*

	WHITE MALE		WHITE FEMALE		COLORED MALE		COLORED FEMALE	
	Gold group	Control group	Gold group	Control group	Gold group	Control group	Gold group	Control group
Number	12	11	8	6	3	2	3	3
Slightly improved	3	0	1	2	1	0	1	0
Definitely improved	4	2	1	0	2	0	2	0
Unchanged	2	4	0	2	0	0	0	1
Slightly worse	1	2	3	0	0	0	0	0
Much worse	0	1	2	1	0	2	0	2
Dead	2	2	1	1	0	0	0	0

Table 2 shows the classification of results according to color and sex

The white female in the control group who died had been chosen as the control for the treated white female who died, the same was true for one "pair" of white males who died, indicating that the arrangement of each group was as much alike as possible

The results in the colored group are directly opposed to the results published by Broch (7) who found that gold had little effect upon the progression of acute exudative tuberculosis in the Negro

Table 3 shows results based on X-ray findings and subjective symptoms

Table 4 shows the observations on the sputum, regarding its bacillary content and its amount All patients had 5 sputum specimens examined by concentration (antiformin) at completion of treatment The three patients in the gold group whose sputum became negative, were negative

for the first time during their treatment, while the two patients in the control group had had negative sputum at different times previously

The striking observation regarding sputum was the decrease in amount found in the gold group. This was marked, varying from one ounce to 16 ounces in some patients

TABLE 3  
*Roentgenological results*

	GOLD GROUP	CONTROL GROUP
Improved	9	2
Unchanged	15	12
Worse	2	8

*Subjective symptoms*

	GOLD GROUP	CONTROL GROUP
Improved	12	6
Unchanged	4	3
Worse	10	13

TABLE 4  
*Observations on sputum*

	GOLD GROUP	CONTROL GROUP
Sputum positive before—positive after	22	17
Sputum positive before—negative after	3	2
Sputum negative before—negative after	1	3
Sputum negative before—positive after	0	0
Amount of sputum decreased	12	4
Amount of sputum unchanged	10	13
Amount of sputum increased	4	5

TABLE 5  
*Haematological picture*

	GOLD GROUP	CONTROL GROUP
Less toxic	9	5
More toxic	7	6
Unchanged	10	11

Table 5 summarizes the haematological findings, based on Schilling's differential count. "More toxic" indicates shift to the left, with a decrease in lymphocytes. By "less toxic" we mean a shift to the right and an increase of lymphocytes. Most of the cases chosen were not

acutely ill, but had had their disease a long time (average 55 years) and their acute symptoms and toxic haematological manifestations had subsided before the treatment. In table 6 the complications are listed. In three patients the gastrointestinal symptoms became so disturbing that treatment had to be discontinued. Mild nausea and vomiting occurred about as frequently as in cases receiving salvarsan, and these milder symptoms are not included in table 6.

In two patients the dermatitis was severe, covering parts of the extremities, the axillae, the chest and back. Treatment had to be stopped in these cases, and saline, glucose and sodium-thiosulphate were given intravenously twice daily for ten days. The eruptions finally cleared in each patient. The third patient developed a slight eruption on the neck and chin, which cleared when treatments were discontinued.

TABLE 6  
*Complications*

	NUMBER OF CASES
Gastrointestinal distress	4
Treatment stopped because of gastrointestinal distress	3
Dermatitis	3
Albuminuria	2
Stomatitis	1
Increased dyspnoea	1
Neuritis (?)	1
Spontaneous pneumothorax	1
Severe chill (due to saline)	6

One patient developed a questionable stomatitis, with some signs of ulceration. She never had salivation or metallic markings on the gums. The dentist thought that most of the ulceration might be caused by her poor teeth.

One patient with a great deal of scarring and fibrosis, had an increase in dyspnoea. This was presumably caused by the deposition of scar tissue and the patient will probably suffer from this complaint to a greater degree, as he continues to control his disease.

One of the patients who had had a skin eruption caused by gold, also developed what we diagnosed as neuritis. After her dermatitis began to clear, she complained of pains in all extremities, usually of a dull character, but sufficient to keep her awake at nights. Various sedatives were given and infra-red rays were applied to the extremities. The pain and discomfort is gradually disappearing under this simple treatment.

Six patients in the gold group suffered a severe chill on one occasion. However, it so happened that three control patients reacted in the same way on the same day. The cause was finally traced to a contamination in the saline used.

Only two of our patients developed albuminuria who had not had it previously. This is an unusually low figure, for most men report this condition occurring in one-half or more of their patients. Smaller dosage and longer intervals between treatments will allow more complete elimination through the kidneys, and prevent an accumulation which might cause damage to the kidneys. McCluskey and Eichelberger found that most of the gold was excreted through the kidneys in one to three days, but that some could still be found in the urine 100 to 130 days after injection (8).

#### SUMMARY AND CONCLUSIONS

I believe there is a very small group of tuberculous patients, probably one or two per cent, in whom gold is indicated. This group consists of patients with bilateral involvement in whom collapse therapy is not indicated. This group would consist of patients with recent involvement, not over one to two years' duration, in whom the disease is acute or subacute. Such a group might be benefited by gold through the drug's property of stimulating scar-tissue formation.

Many other gold preparations are on the market, some older, some newer than gold-sodium-thiosulphate. The amount of gold in these compounds varies greatly, gold-sodium-thiosulphate, being among the stronger in this respect, contains 37.4 per cent gold. It is probable that one of the weaker gold compounds, or some other compound having the same connective-tissue stimulating effect, will come into use. Some drug of this nature that would produce the same effect, but cause fewer complications, would indeed be welcome.

In future treatments I would reduce the dosage considerably, and make 250 mgm. the maximum single dose and 3,000 mgm. the total dose. If more were needed, I would repeat the course. We found that our serious complications did not begin until we gave above 250 mgm. and that the severity of these complications increased as the dosage was increased.

Because of the differences in results published, any attempt to popularize sanocrysin therapy among the general practitioners would be disastrous. Only the men thoroughly acquainted with the treatment of pulmonary tuberculosis should use this drug, and then it would seem



best that treatment be given in a hospital where all necessary material for following the patient is available

What recommendations for or against gold can be given on the basis of our experience? I suspect that I have not improved the opinion held for the use of gold in pulmonary tuberculosis among many of my readers. It appears that the results obtained in our series, as shown by the data presented, were, on the whole, fairly encouraging. However, these results were obtained in a small series and also sufficient time has not elapsed to tell whether continued benefit will be derived or whether those benefited will return to their original condition. I shall not hesitate to use gold in the future, subject, of course, to the limitations just mentioned.

EDITORIAL NOTE Due to the demands upon our space, it was necessary to delete, with the author's permission, the detailed case histories and an elaborate bibliography that formed part of this paper.

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# PNEUMOPERITONEUM IN TREATMENT OF PULMONARY TUBERCULOSIS

A Preliminary Report<sup>1 2</sup>

HAROLD GUYON TRIMBLE<sup>3</sup> AND BUFORD H. WARDRIP<sup>4</sup>

Rapid strides have been made in the treatment of pulmonary tuberculosis during recent years. In conjunction with bed-rest, various lung splinting procedures, used singly and in combinations, have done much to effect rest and promote healing of the affected lung areas. We are familiar with the marked value of such procedures as pneumothorax, oleothorax, phrenic nerve paralysis, apicolysis, intrapleural pneumonolysis, and thoracoplasty when they are used in well selected cases.

However, with all of these measures at our disposal there is still a large group of patients for whom we have had little to offer in the way of an active approach to their therapeutic problem. This group is made up of persons with fairly extensive bilateral pulmonary disease on whom a pneumothorax cannot be established because of adhesions and who cannot well tolerate, either because of age, debility, or for some other reason, any of the more drastic types of collapse therapy.

There is still another group made up of individuals who have had a phrenic nerve paralysis, but who have obtained an inadequate rise of the paralyzed hemidiaphragm. We feel that these individuals would profit by a more adequate rise and splinting of this leaf of the diaphragm.

Probably we have all noted pregnant tuberculous women, who, during the latter months of gestation, have showed a very definite improvement in their pulmonary lesions, only to have these lesions become very much worse following delivery. This observation frequently occasioned comment during staff rounds and there was considerable speculation as to whether the good effect noted during the latter months of pregnancy was the result of hormonal changes, or whether it was from the mechan-

<sup>1</sup> Presented at the annual meeting of the California Tuberculosis Association, Sacramento, California, April 3, 1936.

<sup>2</sup> Presented in part at a session of the Clinical Section at the thirty-third annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 2, 1937.

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ical effect of elevating and splinting the diaphragm. In June, 1934, after reading an article by Dr. Andrew L. Banyai in which he reported a series of 100 cases of pneumoperitoneum which had been used for various pathological conditions, we decided to try to reproduce the mechanical effect of pregnancy by the use of pneumoperitoneum. With the exception of a report of two cases during the previous year by Dr. Ludwig Vajda, practically nothing else was found in the literature regarding the use of pneumoperitoneum in the treatment of pulmonary disease, although pneumoperitoneum and oxyperitoneum have been used for many years in the treatment of intestinal and peritoneal tuberculosis. Pneumoperitoneum was used as a diagnostic measure as early as 1902.

Since starting this work with pneumoperitoneum we have used the procedure in about eighty cases. Statistically our results are not remarkable because it has been employed in instances where, for the most part, there was practically nothing else to offer in the way of active therapy. Frequently the patients were almost moribund before they were seen. On the other hand, some very interesting results have been obtained and we have come to feel that the procedure has a place of therapeutic importance in the treatment of certain types of pulmonary tuberculosis.

As mentioned, the pregnant tuberculous woman suggested to us the possible value of the procedure. Dr. Burgess Gordon of Philadelphia has also tried to reproduce the mechanical effects of pregnancy by a different method, namely by the use of a tailored, snugly fitting abdominal binder. By this means he was able to increase the intraabdominal pressure and thereby cause some elevation and splinting of the diaphragm. The amount of elevation of the diaphragm even during the latter months of pregnancy may be only from 2 to 3 cm., but it is apparently sufficient to be of benefit to pulmonary lesions. If the amount of elevation caused by pregnancy is of value, we can be quite certain that the amount obtained by the use of pneumoperitoneum will also be helpful because as much as two or three times this amount is obtained by the procedure.

The greatest degree of collapse has been obtained by the use of pneumoperitoneum in conjunction with phrenic nerve paralysis. With the addition of subphrenic pressure by pneumoperitoneum, the paralyzed leaf of the diaphragm may rise sufficiently to reduce the volume of the lung to as little as one-third of its original volume. Usually the amount of elevation obtained by this combination is about double that obtained by the use of the phrenic nerve procedure alone.

When a satisfactory pneumoperitoneum is established, there is almost always some limitation of diaphragmatic motion with normal breathing (it may be increased by forced breathing) and often the diaphragm is almost completely splinted. The amount of diaphragmatic rise varies with the individual, but a rise to as high as the third interspace anteriorly on each side has been noted from pneumoperitoneum alone. (See case 4.) We were interested to note that the elevation of the diaphragm was a little greater with the patient in the upright position, also, that if the patient was on one side constantly, the uppermost hemidiaphragm was more affected. Consequently, when pneumoperitoneum is used in conjunction with phrenic nerve paralysis, the patient is kept upon his good side. This, of course, is contrary to the procedure when a patient is placed at postural rest or upon a bolster.

An abdominal binder used in conjunction with pneumoperitoneum has in our experience not caused any greater elevation of the diaphragm with the patient either upright or recumbent, as noted by comparison of X-ray films taken with or without the binder.

The technique might be briefly described by saying that it is very similar to giving pneumothorax refills. Although any point of the anterior abdominal wall may be used as a puncture site, there is definite advantage to a standardized procedure. We have used the following. The patient is placed in a reverse Trendelenburg position. This position is very effective in localizing the abdominal air beneath the puncture site, and as a result, a fluctuating manometer reading is usually obtained almost as soon as air is first introduced. The site chosen for puncture has been just lateral to the left *rectus abdominis* and immediately below the costal margin. This area has the advantage of not overlying any particularly vulnerable viscera and the proximity to the ribs permits the skin to offer some resistance to the needle rather than being pushed in front of it. This latter fact is especially welcome when the abdominal wall is flaccid, such as one is apt to find in a thin multiparous woman.

The site is well anaesthetized by an injection of 3 cc to 5 cc of one per cent procaine down to the peritoneum. An ordinary pneumothorax needle (2-inch, no. 19 gauge, short bevel) is used for the introduction of air and the procedure is identical with that used for pneumothorax. With the initial fill an oscillation of the manometer may not be obtained, but one can determine when the needle has entered the peritoneal cavity by the lack of tissue resistance in front of it and the ease with which the air flows through the needle. Following the initial in-

jection of air there may be some discomfort and shoulder pain for a few days, but if the pain is severe it can be relieved by elevating the foot of the bed which removes the air from the lower surface of the diaphragm. After pneumoperitoneum is established, the manometer readings are almost always positive and may go as high as plus 7 cm, plus 5 cm (water manometer) or more. The oscillations of the manometer are narrow as compared to those encountered with pneumothorax, and are paradoxical. The amount of air given should be comparatively small with the first few refills to avoid undue discomfort. Thereafter the amounts of the refills vary from 200 to 500 cc twice a week, or 500 to 1000 cc once a week. This, of course, varies with the rate at which the air is absorbed. Because of a relatively large area of peritoneal surface, the air from the peritoneal cavity is absorbed more rapidly than from the pleural space.

As with pneumothorax, complications can and do arise, though in

#### PLATE 1

Fig 1 Normal chest at eight months gestation. Dotted lines indicate level of diaphragm before pregnancy.

Fig 2 Normal chest of patient who was examined as a tuberculosis contact.

Fig 3 Chest of same individual who subsequently developed tuberculous enteritis and peritonitis with resulting tympanitis. Film illustrates marked elevation of the diaphragm resulting from intraabdominal pressure. Dotted lines indicate original level.

#### Case 1 J P, age 33 Italian housewife

Fig 4 August 1, 1934 Patient first seen at this time with extensive bilateral lesions. A right artificial pneumothorax started.

Fig 5 September 14, 1934 Selective collapse of right lung by pneumothorax. Left pneumothorax attempted but unsuccessful because of adhesions. Pneumoperitoneum started in December, 1934, to splint the left lung.

Fig 6 February 11, 1936 Pneumothorax and pneumoperitoneum effective in controlling lesion in right lung. Pneumoperitoneum has resulted in marked elevation and splinting of both leaves of the diaphragm. There has been much clearing of the left lung field. Sputum is diminished, though still positive, and patient has shown much clinical improvement.

Case 2 Wm J E, age 47 Irish American salesman. Had pleurisy in 1932. Onset of symptoms of present illness in October, 1935. First seen in January, 1936.

Fig 7 December 30, 1935 Acute exudative lesion in upper portion of the left lung. Sputum positive. Attempts to establish a left artificial pneumothorax unsuccessful.

Fig 8 February 24, 1936 Showing elevation of the left hemidiaphragm following temporary paralysis of left hemidiaphragm done on February 14, 1936.

Fig 9 March 13, 1936 To augment rise of the left hemidiaphragm a pneumoperitoneum was started February 24, 1936. The patient has been kept on his right side to localize air beneath the left leaf of diaphragm. Pneumoperitoneum has almost doubled the degree of elevation of the left hemidiaphragm. Note clearing of the left lung field.

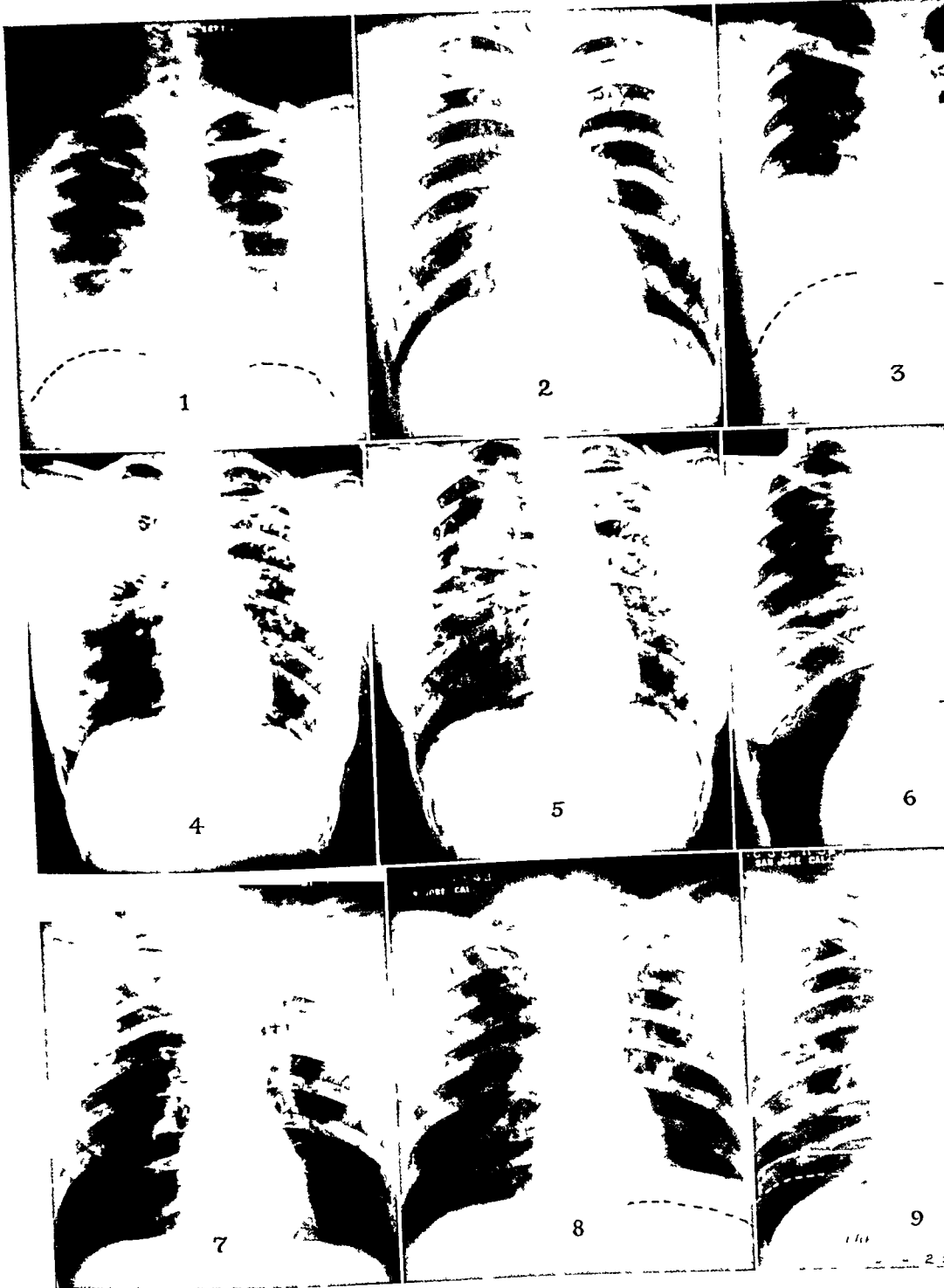


PLATE 1

our series these have been few. There seems to be little danger of puncturing a gut unless a loop of bowel should be adherent to the anterior abdominal wall at the site of the puncture. To our knowledge, this complication has not occurred in our series. Fluid is encountered in a small percentage of cases. There has been one case of adhesive peritonitis which eventually completely obliterated all free space. This caused the patient practically no discomfort at the time, and although it occurred over a year and a half ago, she has suffered no ill effects. Her pulmonary lesions are much improved. Moderate weight loss is rather frequently encountered. One patient died of an air embolus.

## PLATE 2

### Case 3 H. D., age 43 White male, musician

Fig 10 August 20, 1934 Extensive bilateral pulmonary lesions more extensive on the right. Right artificial pneumothorax from January to October, 1935. Collapse entirely inadequate.

Fig 11 September 18, 1935 Right phrenic nerve avulsed March 1935. Good rise of right hemidiaphragm. Splinting of the right lung still considered inadequate and pneumopentoneum was started in October 1935. Pneumothorax abandoned. Sputum still positive.

Fig 12 February 11, 1936 Note additional rise following pneumopentoneum (4 months). Amount of sputum reduced and is now negative for acid fast organisms. Film illustrates additional rise that can be obtained from pneumopentoneum. Note the presence of peritoneal fluid.

### Case 4 R. R., age 24 White student nurse

Fig 13 August 15, 1934 The patient was at bed rest from December 1933, to April 1934. Pneumothorax was attempted without success in April 1934. Right phrenic nerve was crushed in January 1935. Poor rise. Cavity still open in June, 1935.

Fig 14 February 16, 1936 Pneumopentoneum started in June, 1935 and continued to date. Pneumopentoneum has resulted in marked splinting and elevation of both leaves of the diaphragm. Dotted lines mark the original level. The cavity in the right subclavicular region is closed. Sputum is negative.

### Case 5 Robert R. age 31 White male newsboy

Fig 15 September 26, 1931 The patient was first seen at this time with an extensive involvement of the right lung. Pneumothorax not possible because of adhesions.

Fig 16 June 9, 1933 Right phrenic nerve avulsion in January 1933. Good rise as shown. However, it was not effective in controlling the lesion alone.

Fig 17 August 28, 1934 Upper stage thoracoplasty July 1933. This with phrenic nerve avulsion was temporarily adequate in controlling the lesion. Sputum negative. He was discharged in February 1934 and followed at the clinic. Note the lower level of the diaphragm.

Fig 18 September 12, 1935 Developed new lesion with large cavity at the right base. Sputum positive. Patient was readmitted and a pneumopentoneum was started in October, 1935.

Fig 19 February 1936 Note the rise of the right hemidiaphragm with pneumopentoneum (4 months). Sputum is negative. Cavity is closed.

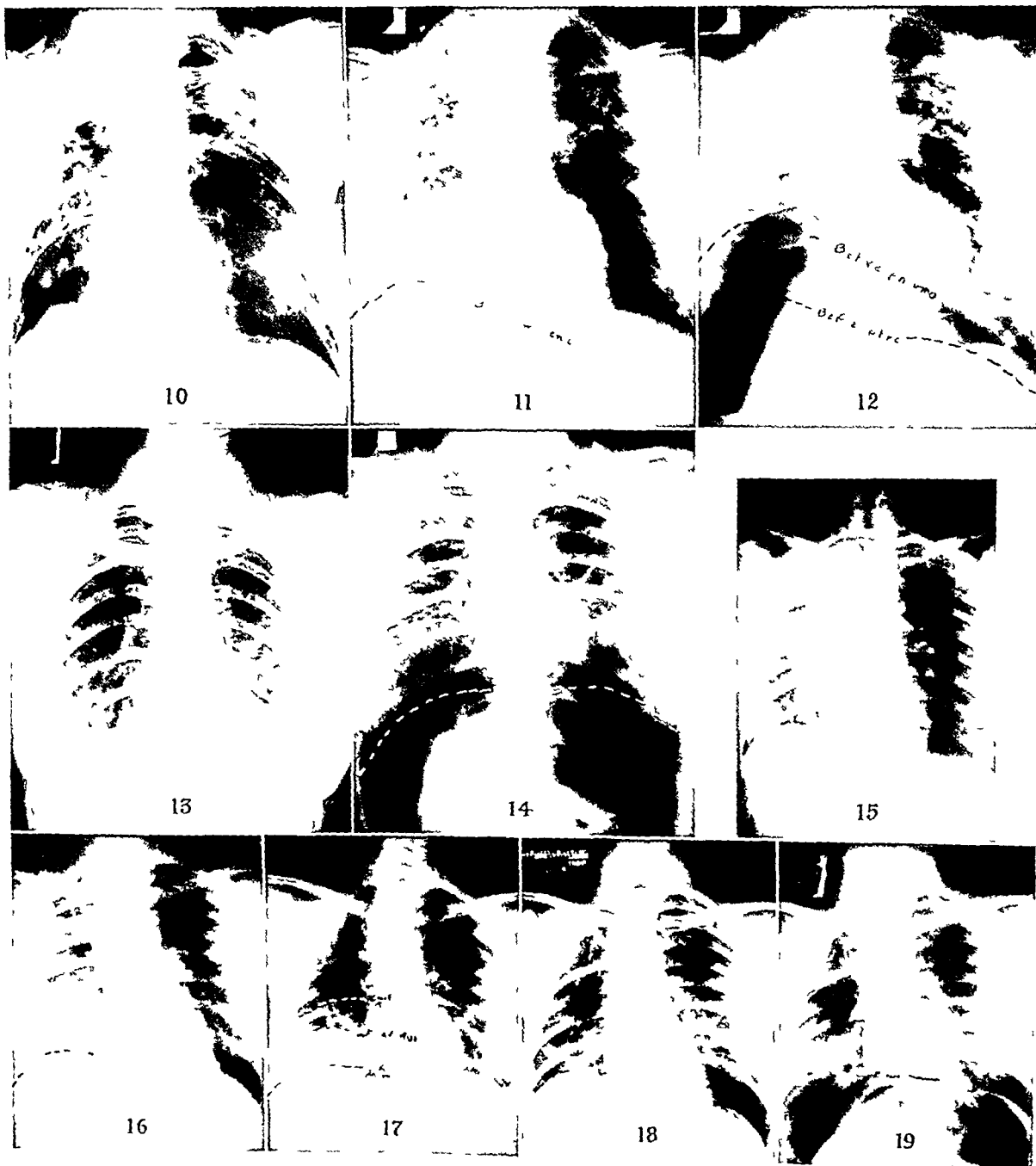


PLATE 2



This should be called a preliminary report because the procedure has not been used sufficiently long to determine its true therapeutic value. To date, however, three far-advanced cases have been made sputum-negative. Cough and sputum have frequently been diminished and the patient made more comfortable. Cavities which have failed to close by any other available procedure, have been closed by pneumoperitoneum. This is particularly true of basilar cavities. In one case it was effective in closing a large subclavicular cavity which had been present for two years.

The psychology on the group of patients for whom previously there was very little to offer, has also been of marked benefit.

### CONCLUSIONS

The beneficial effect of the latter months of pregnancy upon pulmonary lesions is apparently due to the mechanical effect of elevating and splinting the diaphragm. The same effect can be obtained to a much greater degree by the use of pneumoperitoneum.

It has a particularly valuable application in patients who have a fairly extensive bilateral pulmonary tuberculosis and who cannot be given pneumothorax because of extensive adhesions and who cannot tolerate more drastic procedures of collapse therapy. It is also a valuable adjunct in obtaining a greater rise of the paralyzed hemidiaphragm.

The authors wish to express their appreciation for the kind assistance rendered by Drs. C. Bush, C. Mason, I. Gourley, R. Libby, and Hart of the Alameda County Institutions and Miss M. Schuler of Alum Rock Sanatorium.

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# THE EFFECT OF SPLENECTOMY ON TUBERCULOUS INFECTION IN MICE<sup>1</sup>

JESSIE MARMORSTON

The reports of the effects of splenectomy on resistance to infection are contradictory. The mass of evidence points, however, to a definite depression in both the natural and acquired resistance of animals to spontaneous or induced infection with certain microorganisms following splenectomy.<sup>2</sup>

Bardach (2) observed that splenectomized dogs succumbed in a very high percentage (80 per cent) of instances to an induced anthrax infection. Only 20 per cent of the controls died. Morris and Bullock (3) studied the effects of splenectomy in immature and mature rats on the mortality to spontaneous infection with *Bacterium enteritidis* (Gaertner) during the course of an epizootic in their laboratory stock. Their experiments suggest that removal of the spleen lowers the resistance of the rat to the spontaneous infection. In view of the significance of the experiments, it is regrettable that no mention is made in the author's report as to the presence or absence of anaemia following splenectomy in the rats used. During the past few years it has been demonstrated that *Bartonella muris* anaemia follows removal of the spleen in almost all strains of rats used for laboratory purposes (4) (5) (6) (7) (8).

The factor of latent infections was eliminated in the experiments of Marmorston (9) on the effect of splenectomy in mice to a subsequently induced *Bacterium enteritidis* (Gaertner) infection. Marmorston observed that in a strain of mice highly resistant to bacterial infection, the removal of the spleen depressed the natural resistance to a subsequently induced infection with *Bacterium enteritidis*. In a strain of mice highly susceptible to bacterial infection the removal of the spleen did not affect the natural resistance to a subsequently induced infection with *Bacterium enteritidis*. Kurlow (10), Courmont and Duffau (11), observed in rabbits no definite effect of splenectomy on induced infections with

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<sup>2</sup> For a detailed review on this subject see monograph by Perla and Marmorston (1).

staphylococcus, pyocyaneus, streptococci and chicken-cholera. Their experiments, however, are difficult to evaluate because the number of animals was small.

Splenectomy in rats, dogs, cats and rabbits, depressed the resistance of these animals to a subsequent infection with *Trypanosoma brucei* (Bradford and Plimmer (12), Davis (13)). Regendanz and Kikuth (14) found that *Trypanosoma lewisi* infection in splenectomized rats was more severe than in normal rats. Perla and Marmorston (15) observed the effect of splenectomy on infection with *Trypanosoma lewisi* when the operation was performed at various intervals before infection, and determined the effect of autoplasmic splenic transplants on the infection in splenectomized rats. The rats used were carriers of *Bartonella muris* and splenectomy in these rats resulted in *Bartonella muris* anaemia. Reproductive forms of the parasite were observed several days longer in the splenectomized than in the normal rats, and the duration of the infection in the former rats was twice as long as in the normal groups. Forty-eight days after splenectomy the infection with *Trypanosoma lewisi* is less severe than in the early period. Apparently some compensatory mechanism has been established, but this is less effective in combating infection than the normal splenic tissue. Splenic autotransplants introduced four weeks prior to splenectomy raise the resistance of rats to a subsequent *Trypanosoma lewisi* infection. Taliaferro, Cannon and Goodloe (16) observed the course of *Trypanosoma lewisi* infection in splenectomized rats, noninfected with *Bartonella muris*. Prolongation of the infection was observed in splenectomized rats of both carrier and noncarrier stock, but the period during which reproductive forms of parasites were observed in the blood was not increased in the splenectomized rats of noncarrier stock.

Foot (17) studied the effect of splenectomy on bovine tuberculosis in rabbits. The operation was performed two weeks before infection. The rabbits were injected intravenously with 0.2 mgm of a culture of bovine tubercle bacilli two weeks old. The lungs of the splenectomized rabbits contained a great number of discrete, firm miliary tubercles, whereas in the control group, the lungs contained areas of caseous pneumonia. The course of the disease was not conspicuously altered, the actual differences in the length of life after inoculation in the splenectomized and normal animals being less than one week. The liver showed more extensive lesions in the operated than in the control animals.

Lewis and Margot (18) described experiments supporting their opinion

that removal of the spleen in mice greatly increased resistance to infection with bovine tuberculosis, induced two weeks after operation. The infection in splenectomized mice, they state, tended to remain localized as contrasted with an almost septic type of disease which occurred in the normal animals. The animals in each group that lived more than 30 days often had "exudative" lesions. This apparently increased resistance was diminished by the feeding of fresh spleen of mouse or sheep. (In our own experience, fresh spleen is irritating and causes profound gastroenteritis.) Recently Watson (19) has studied the effects of aqueous extracts of raw spleen on the course of experimental tuberculosis of the human type in guinea pigs, and comes to the conclusion that the duration of the disease is considerably prolonged by repeated injections of extract. Details concerning the method of extraction, the animal from which splenic tissue was obtained and the amounts administered are not mentioned.

The purpose of the experiments reported in this communication was to study the effect of splenectomy in mice on natural resistance to tubercle bacilli.

#### *Effect of Splenectomy in Mice on the Course of an Induced Infection with Bovine Tubercle Bacilli*

A series of 28 adult mice was divided into three groups. Twelve were splenectomized with aseptic technique, through a vertical incision in the left upper quadrant of the abdomen, in eight a laparotomy was performed and the spleen exposed and replaced, and eight were used as normal controls. One week after operation, all were infected intraperitoneally with 0.1 mgm. of bovine tubercle bacilli.

The changes induced in mice by a tuberculous infection, bovine or human, are primarily limited to the site of inoculation, the lungs, the liver and the lymph nodes. Tubercles such as are found in other mammals do not occur in the mouse and only a few epithelioid cells may appear in the liver. Massive necrosis of liver tissue may occur without previous tubercle formation. Proliferation of Kupfer cells and periportal accumulations of cells resembling lymphocytes are the usual changes found in the liver. The lesions in the lung are pneumonic in character, and both polymorphonuclear leucocytes and large fat-laden macrophages accumulate in the alveoli. The lesions are more severe after infection with the bovine than with the human type of tubercle

bacilli. The local peritoneal lesions were slight in both groups, some thickening of the omentum and a small caseous node in the mesentery were occasionally observed.

When an animal died in any group, one of each of the other groups was killed and the lesions compared. The experiment was terminated three months after the infection was induced and the surviving animals were killed and examined at that time. The mice used in this and the following experiment were carriers of *Eperythrozoon coccoides*, *Bartonella muris* and *Klossiella muris*.

There was a definite decrease in the resistance of the splenectomized mice (see table 1). Seven of the twelve splenectomized mice succumbed in 18 days, 46 days, 48 days, 63 days, 69 days, 74 days and 76 days.

TABLE 1

*The effect of splenectomy in mice on the course of a subsequently induced infection with Myco bacterium tuberculosis (Bovine Raval)*

	NUMBER OF MICE	NUMBER OF MICE THAT DIED SPONTANEOUSLY OF TUBERCULOSIS	NUMBER OF MICE INFECTION ABSENT	EXTENT OF DISEASE AT THE END OF EXPERIMENTAL PERIOD		
				Slight	Moderate	Severe
Splenectomy	12	7	0	4	2	6
Laparotomy	8	0	2	4	2	0
Normal controls	8	0	3	3	2	0

respectively, after the infection was induced. The mice in which a laparotomy was performed showed about the same extent of tuberculosis as the normal controls.

The distribution of the disease process was noteworthy. The lungs, lymph nodes and liver were more extensively involved in the splenectomized group than in the normal.

*Effect of Splenectomy in Mice on the Course of an Induced Infection with Human Tubercle Bacilli*

A series of 18 mice was divided into three groups. Eight were splenectomized, in six a laparotomy was performed and four were used as normal controls. All the mice were infected with 0.1 mgm. of a human type of tubercle bacillus intraperitoneally.

None of these animals died spontaneously, but all were killed at the end of three months.

In these animals as in those that received bovine tubercle bacilli, the lungs, lymph nodes and liver were more extensively involved in the

splenectomized group Microscopically the smaller lesions were primarily accumulations of lymphocytes with little or no giant cell formation and no caseation Some alveoli contained large lipid-laden macrophages

The kidneys in three of the splenectomized mice were large, yellowish-brown in color and had gray patches in the cortex In microscopical sections intense infection with a coccidium (*Klossiella muris*) was found All the splenectomized mice showed similar microscopical changes in the kidneys In the control group only an occasional animal was infected with *Klossiella muris* as determined by the microscopical appearance of the kidneys

TABLE 2

*The effect of splenectomy on the course of a subsequently induced infection with Mycobacterium tuberculosis (Human H-37)*

	NUMBER OF MICE	NUMBER OF MICE, INFECTION ABSENT	EXTENT OF THE DISEASE AT THE END OF THE EXPERIMENTAL PERIOD*		
			Slight	Moderate	Severe
Splenectomy	8	1	0	3	4
Laparotomy	6	1	3	0	1
Normal controls	4	1	2	1	0

\* The mice were all killed at the end of three months

*The Effect of Splenectomy in Mice Free from Eperythrozoon coccoides, Bartonella muris and Klossiella muris on the Course of a Subsequently Induced Infection with Bovine Tubercle Bacilli*

In the course of the first two groups of experiments it became apparent that the mice used for these studies were carriers of latent infections influenced adversely by splenectomy Latent infections with three microorganisms were found *Eperythrozoon coccoides*, a parasitic infection of the red cells that did not produce an anaemia and that manifested itself only after the removal of the spleen (20) (21) (22), *Bartonella muris*, producing a mild infection in the mouse without anaemia and becoming manifest toward the close of infection with *Eperythrozoon coccoides*, (22), and *Klossiella muris*, a coccidium parasite producing lesions of the kidney, perhaps intensified by splenectomy (23)

The effect of splenectomy on the course of bovine tuberculosis was studied in a stock of mice found to be free from these infections<sup>3</sup>

<sup>3</sup> These mice were kindly given us by Dr Leslie T Webster of the Rockefeller Institute for Medical Research

Eighty four mice of this stock were divided into three groups 30 were splenectomized, in 25 a laparotomy was performed and 29 were used as controls All were injected intraperitoneally one week after operation with 0.1 mgm of a culture of *Mycobacterium tuberculosis* (Bovine Ravenal)

Blood smears were examined every second day for the presence of *Eperythrozoon coccoides* and *Bartonella muris* and were found negative

The kidneys of all mice were carefully examined for the presence of *Klossiella muris* and in no instance was this infestation found

Of 54 normal and operated control mice only 6 mice died spontaneously of tuberculosis at 90, 95, 98, 125 and 154 days respectively At the end of 164 days after injection, all those that had survived were killed and

TABLE 3

*The effect of splenectomy in mice free from latent infections on the course of a subsequently induced infection with Mycobacterium tuberculosis (Bovine Ravenal)*

	NUMBER OF MICE	NUMBER OF MICE THAT DIED SPONTANEOUSLY OF TUBERCULOSIS	EXTENT OF DISEASE IN MICE KILLED AT END OF EXPERIMENTAL PERIOD (KILLED AT END OF 164 DAYS)		
			Slight	Moderate	Severe
Splenectomy	30	11	0	6	13
Laparotomy	25	4	10	4	7
Normal controls	29	2	15	7	6

autopsied Of the 48 killed at this time, in 35 the infection was slight, in 11 it was moderate and in 13 it was severe and extensive

Of the 30 splenectomized mice, 11 died spontaneously at 40, 45, 48, 52, 63, 65, 68, 73, 87, 106 and 135 days respectively and the surviving 19 were killed at the end of the experimental period Of the 19 surviving mice which were killed, in no instance was the disease mild, as determined by the extent of the lesions, in 6 the disease was moderate but in 13 it was extensive

The tuberculous lesions in the liver and lungs were more severe in the splenectomized animals than in the nonsplenectomized mice

These results confirm the earlier experiments performed in mice that were carriers of latent infections In mice free of *Eperythrozoon coccoides*, *Bartonella muris* and *Klossiella muris*, splenectomy lowers the natural resistance to a subsequently induced infection with *Mycobacterium tuberculosis* (Bovine strain)

## SUMMARY AND CONCLUSIONS

Removal of the spleen in mice diminishes natural resistance to a subsequently induced infection with human or bovine tubercle bacilli

The results of experiments were essentially the same in mice that were carriers of latent infections with *Eperythrozoon coccoides* and with *Bartonella muris* and those that were free from these infections

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# THE CERTIFIED DIAGNOSIS OF TUBERCULOSIS

Further Practical Studies on the Detection of Tubercle Bacilli

MORRIS GREENBERG<sup>1</sup> AND MAURICE L. COHEN

In 1928, Corper (1) emphasized the significance of methods for demonstrating tubercle bacilli for the certified diagnosis of tuberculosis. He showed the relative lack of delicacy of the microscopical examination of the stained smear, which has the advantage of speed over guinea-pig inoculation and culture methods. The latter two methods are capable, with equal efficiency, of disclosing small numbers of tubercle bacilli in specimens; the culture, however, possessing the advantage of economy and of revealing tubercle bacilli as such (2).

In spite of the numerous valuable contributions on the subject of cultural diagnosis within the past decade, textbooks and various reports still deal with this subject in vague terms and include materials and media proved obsolete at least ten to twenty years ago. Some of these are entirely misleading in the light of fundamental facts. For illustration, a recent note (3) advises that 'as sputum frequently contains many other micro-organisms one can destroy them for the most part by treating it with 4 per cent antiiformin. After an hour the material is centrifugated, and the sediment planted on laboratory mediums. Antiiformin may be dispensed with if Petroff's medium which contains gentian-violet is used. This inhibits the growth of micro-organisms other than tubercle bacilli, and therefore permits one to plant sputum directly on it.' Suffice it to say, antiiformin is entirely unsuited for recovering small numbers of tubercle bacilli; Petroff's medium cannot be used without first destroying contaminants by means of sodium hydroxide or other suitable reagents, and finally the amount of gentian-violet in this egg medium retards the growth of small plantings of tubercle bacilli (4) (5). This medium served a very good purpose when introduced in 1915, but progress has proved it inadequate.

Now and again, practice requires that we evaluate various techniques and methods, primarily to disclose the latitude permitted and also what recommendations may be made as to the essentials and nonessentials in

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the routine of the sanatorium and the clinic. It is obvious that striking differences are disclosed between the microscopical examination of the stained smear and the guinea pig or culture. Can we expect striking differences in results between the various methods of staining smears, and where in this category can concentration methods be placed for the purpose of practice? It was the object of this study to elucidate this question by comparative experimental observations.

Among those cumbersome techniques which must again be evaluated frequently for practice are the so-called concentration methods, usually time-consuming and fraught with numerous possibilities for confusion. Within recent years only isolated techniques on such methods have been described and reported. Among these are included a dilution-flotation test (6) which is highly recommended for practice. This method which makes use of dilution and flotation by means of xylol, benzene, gasoline, and ligroin, and a mechanical shaking device to disperse the hydrocarbon through a diluted, sodium-hydroxide digested specimen, claims an efficiency 200 times better than the microscopical examination of the stained smear and alleges to reveal the presence of as few as 1,000 bacilli in a 24 hour specimen. It is stated "such results approach quite closely the recognized sensitiveness of guinea pig inoculation as well as the not too well determined sensitiveness of the culture method."

In order to evaluate the various smear methods, concentration and culture methods, the following comparative tests were made on the same natural specimens:

- 1 Various staining methods were compared, including the Ziehl-Neelsen and Spengler methods
- 2 Comparison of the stained smear with the dilution-flotation method
- 3 Comparison of the smear with the dilution-flotation and culture. In addition, comparison and tests were also conducted with specimens prepared for the purpose by adding graded amounts of fine suspensions (7) of tubercle bacilli to negative sputa

It is not the purpose of this report to give elaborate details of all the experiments performed but rather to present the pertinent results in a few tabulations that will prove of practical value to others either in pursuing further studies or in applying these findings to practice.

In one of our experiments to determine the value of counterstains in increasing the efficiency of the findings, 123 specimens of sputum were examined by the direct smear method. The slides were prepared in the

usual manner and one-half of each slide was counterstained with methylene-blue and the other half with picric acid. Each half was examined for at least fifteen minutes unless ten or more bacilli were found in a shorter period of time. The results were, briefly methylene-blue side, 39 positives, picric acid side, 48 positives. These findings verify those of earlier observers who maintain that picric acid counterstaining yields a higher percentage of positive findings. In addition, it was noted that in the majority of cases more bacilli were found per field in the picric acid stained preparations. However, methylene-blue has the advantage of its differential staining quality, enabling the observer to distinguish cell structures, bacterial forms, etc., while picric acid merely acts as a diffuse stain. Where specimens are to be examined for tubercle bacilli alone, picric acid possesses advantages over methylene-blue as a counterstain.

In another experiment, the microscopical examination of the stained smear (carbol-fuchsin) with picric acid counterstain was compared with the dilution-flotation method on natural specimens from sanatorium patients. The dilution-flotation method used was as follows: a 24- to 72-hour specimen of sputum was collected in a sterile receptacle, a particle of this material was selected for examination by the direct smear and a 20 cc sample was used for flotation test by placing it in an 80 cc clean sterile test tube fitted with a clean sterile rubber stopper. To this was added an equal volume of 0.5 per cent sodium-hydroxide solution and the mixture shaken and digested in a water bath at 56°C for 30 minutes, following which it was diluted to 60 cc with sterile distilled water and 1 cc of xylol was added. The mixture was shaken in an electrical shaking machine for 20 to 30 minutes and the tubes were permitted to stand until the opaque layer of xylol rose to the top. Invariably good separation occurred but occasionally when a xylol layer did not form the supernatant fluid was withdrawn, the specimen rediluted and shaken again. Smears from the entire xylol layer were made, using albumin fixative on the slide. After drying and fixing, ether was used to remove the excess xylol before staining. In a separate control experiment performed for the purpose of testing whether xylol or chloroform would change the acid-fast staining properties of tubercle bacilli, it was found that even prolonged contact with these reagents had no appreciable effect on the acid-fast properties.

In this series in which 314 natural specimens, including sputa, pleural fluids, etc., were examined by the direct smear and the above dilution-flotation method, the following results were obtained by the direct

smear, 55 were positive, by the dilution-flotation method, 59 were positive. Those positive by both methods were 42, by the direct smear alone, 13, and by the dilution-flotation method alone, 17, giving a total of 72 positives by both methods. When considering the large number of specimens examined (314), and the fact that only four more gave positive results by the dilution-flotation method as compared with the simple direct smear examination, it would hardly suggest a practical advantage to use such a method.

The divergent results between the two methods are readily understood when it is recognized that natural tuberculous specimens are in their very

TABLE 1

*Microscopical demonstration of tubercle bacilli in sputa to which graded suspensions of tubercle bacilli have been added. Comparative results of five methods*

NUMBER OF TUBERCLE BACILLI PER CC OF SPECIMEN*† (8)	DIRECT SMEAR METHOD		DILUTION FLOTATION* TEST*	CHLOROFORM SEDIMENT (9) TEST*	NaOH DIGESTION CENTRIFUGATION AND EXAMINATION OF SEDIMENT*
	Methylene blue counterstain	Picric acid counterstain			
100,000,000	5†	50	1000	1000	1000
10,000,000	1	8	300	100	100
1,000,000	0 02	0 07	5	1	2
100,000	0 03	0 06	0 15	0 06	0 1
10,000					
1,000					
100					
0					

\* 10 cc. of sputum were used in each of the concentration tests

† The numerals indicate the average number of bacilli found per field

‡ 1 mgm. of bacillary mass contains about one billion tubercle bacilli in fine suspension

nature irregular and nonhomogeneous so far as their content of tubercle bacilli is concerned

In another experiment, 113 specimens, negative by the microscopical smear and dilution-flotation test, proved positive in 25 cases by culture alone. The culture method used was the sulphuric-acid-treatment potato medium (1) (two tubes planted from each specimen) and inspissated egg-yolk medium (8) (three tubes planted from each specimen). This experiment carefully performed from a comparative standpoint, all tests being carried out on the same specimen, again proved the efficacy of the culture over these other methods. It is interesting to note that in practically all the reports in the literature concerned with the demonstration of tubercle bacilli in the gastric washings or faeces

of children suspected of tuberculosis, either the culture method or the guinea-pig test was depended upon for diagnosis

In order to obtain further information regarding particularly the quantitative relations between the results of the rapid microscopical smear examinations and various so-called concentration methods, these methods were compared experimentally on specimens which were artificially prepared to contain known amounts of fine suspensions of tubercle bacilli. The bacillary suspensions were well mixed with the sputum by prolonged shaking in an electrical shaking machine to insure as uniform and equal distribution as possible. Uniform portions were submitted to the different tests with the results recorded in table 1.

An examination of the results recorded in table 1 indicates that when large numbers of bacilli are present in a sputum, there are wide variations in the individual findings obtained. However, it is evident that, when graded amounts of bacilli are added to a sputum and this sputum is examined by the commonly used laboratory procedures as well as concentration or dilution-flotation tests, the point of extinction does not vary by a difference of a dilution of ten but occurs rather uniformly at a point approximating the presence of about 100,000 bacilli per cubic centimetre of specimen. This agrees well with the findings recorded previously by Corper (1) in earlier studies on the certified diagnosis of tuberculosis.

#### DISCUSSION

It is almost a dictum in medicine that the value of practical test or method of diagnosis or prognosis is dependent upon at least one or both of the following characteristics: it should be simply and speedily performed or it should make available information on a disease or group of diseases not obtainable by any other procedure. When considering the certified diagnosis of tuberculosis, it appears that there are three procedures to be evaluated in the light of our present-day knowledge. One of these, the microscopical examination of the stained smear, has held a favored place in private and sanatorium practice for speed and simplicity from the date of discovery of the tubercle bacillus over fifty years ago, although its limitations were not always recognized. Another, the use of the guinea pig as a diagnostic test animal, has enjoyed almost as long but not as universal popularity because of its selective specific accuracy for the examination of certain types of material (genitourinary specimens) and it supplied in delicacy and specificity what it lacked in

speed and simplicity Finally, after numerous futile efforts, culture methods were developed which under carefully performed quantitative tests proved to be equal in delicacy to the guinea pig as a test and possessed certain definite advantages both economically and practically During the period of development of culture methods to a point of high efficiency, there have been numerous attempts to employ some means of increasing the number of bacilli in a specimen to be examined microscopically in the stained smear by concentrating the bacilli in such a specimen by either attempting to concentrate them in a sediment or by collecting them in an intermediate zone of a watery and oily layer, or by floating them on a brine or by a combination of dilution and flotation Such procedures usually involve time and multiple manipulations with the added possibility of introducing the universally present acid-fast saprophyte to confuse the value of the test That the guinea pig and culture when properly used surpass both the microscopical smear examination and so-called concentration methods is evident from most of the recently performed empiric tests with natural specimens Thus, a recent report (10) uses 100 sputa "in which *B tuberculosis* had previously been demonstrated in the sputum but which had been negative by direct smear on three consecutive occasions" and finds the gasoline concentration test (GCT) and culture positive in 31, the GCT positive and culture negative in 6, and culture positive and GCT negative in 18 In 100 cases in which *B tuberculosis* had never previously been demonstrated in the sputum, both were positive in 6, GCT positive and culture negative in 3, and GCT negative and culture positive in 8 This is illustrative of numerous examples in which the actual quantitative value of the methods used was unknown and in which tests were performed only on empiric specimens which, because of their very nature, were bound to give inconsistent and irregular results, yet the superiority of the culture is evident in both series of specimens tested, while the original proponent of the concentration method used indicated its equivalence to culture methods When, however, tests are performed, as was done in the experiments recorded in our study, with specimens to which graded amounts of bacillary suspensions are added, it is evident that concentration or dilution-flotation methods do not achieve a concentration of ten to one over the microscopical smear examination alone (see table 1) (11) while culture and guinea-pig tests are approximately over a thousandfold more delicate than these tests, although they are admittedly slow in disclosing the desired findings

## SUMMARY

1. In the majority of cases, picric acid as a counterstain proved superior to methylene-blue in the examination of sputa for acid-fast bacilli, although methylene-blue possessed the advantage of distinguishing cell structures and other bacterial forms

2 The microscopical examination of the stained smears of 314 tuberculosis specimens proved equally efficient to a dilution-flotation method

3 The culture, properly performed, is superior to microscopical methods In an experiment performed on 113 negative specimens by direct smear and dilution-flotation test, 25 proved positive by culture

4 Control experimental tests with negative sputa to which were added small graded amounts of fine suspensions of tubercle bacilli revealed that there is not a 10 to 1 concentration of bacilli attained by various concentration methods as compared to direct smear examination

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## BOOKS

WILLIAM SNOW MILLER *The lung* Pp xiv + 212, with 152 illustrations, 20 of them colored, Charles C Thomas, Springfield, Illinois, 1937, cloth, \$7 50

By B F KINGSBURY

It is entirely fitting that a scientist should bring together in a single volume the significant results of a life-time of work. This has been done in the present volume upon "The Lung" by Professor emeritus William Snow Miller of the University of Wisconsin, who through a period of nearly fifty years has devoted much of his research time to an elucidation of the anatomy of the lung. This little volume is not, however, a mere compilation of Doctor Miller's numerous contributions to an understanding of the structure of the lung. It is a logical and orderly progression through twelve chapters, from a concise statement of the gross anatomy to a consideration in the final chapter (xii) of the structural and functional unit which Miller regards as the primary lobule.

The work is illustrated by 152 figures, 20 of them in colors, carefully selected. Many of them are original or reprinted from figures previously published by the author. The paper and printing are excellent, typographical errors few. The context is supplemented by a bibliography of 222 titles, and the whole is fully indexed, author and subject.

The twelve chapters deal with (1) the lungs, (2) the trachea and bronchi, (3) intrapulmonary bronchi and bronchioles, (4) the air spaces, (5) the blood vessels, (6) the lymphatics, (7) the pulmonary lymphoid tissue, (8) the nerves, (9) the pleura, (10) key points, (11) historical sketch, and finally (12) the acinus. In this succession of chapters, the presentation is so logically developed that it is difficult for the reviewer to select any one feature for emphasis.

Aside from the structural plan of the lung so well portrayed by the figures 54 and 114, may be mentioned the tracheal and bronchial musculature, the elastic tissue of the lung and pleura, the structure of the pleura and the lymphatic drainage. The old and vexed question as to the lining of the respiratory chambers (alveolar ducts, atria, alveolar sacs, alveoli), recently revived, is decided by Doctor Miller in favor of a continuous epithelium. Non-nucleated plates, however, are not present. The source of "alveolar phagocytes" is not fully discussed but an epithelial origin is discounted. "Foam cells" within the alveolar spaces are regarded as desquamated cells from the respiratory epithelium. Pores in the alveolar wall are artifacts or results of



such cell desquamation. Significant is the discussion of the relation of the bronchial and pulmonary circulations.

As a concise and accurate presentation by a master of the subject, the book will be a valuable addition to the library of the clinician and pathologist, as well as the anatomist and histologist. From an even superficial examination of this work, it is obvious that for Doctor Miller the structure of the lung is far from being a closed chapter. Further contributions by him may be confidently expected.

HENRI JOLY *La collapsothérapie hypotensive appliquée au traitement médico-chirurgical de la tuberculose pulmonaire*. With 10 schemas and 36 figures in the text, pp 314, Gaston Doin & Cie, Paris, 1936, paper, 50 fr.

By J. BURNS AMBERSON, JR.

Practitioners of collapse therapy by pneumothorax or more radical methods should possess technical skill and thorough knowledge of pulmonary mechanics and of the pathology of tuberculosis. Skill comes more easily than the knowledge, and both more easily than the wisdom with which they should be applied. Those who subscribe to this view will find in Joly's book much substance for thought, those who do not might well read it for the beginning of their enlightenment. The treatment of the subject is thoroughly scientific and is not colored by enthusiasm. The fundamental premise is that hypotensive pneumothorax, affording relaxation of the lung, is physiologically rational and clinically effective in properly selected cases, whereas compressive pneumothorax is not just the reverse but even worse, since it favors progression of the disease in the opposite lung, pleural effusions and rupture of the pleura. Such condemnation of compressive pneumothorax is too severe, because gentle compression (+2 to +6 or +8 cm. water) maintained by frequent refills avoids undue hazards and often suffices to accomplish the desired result. Nevertheless, in a logical and comprehensive discussion, the author makes out a strong case for the efficacy of low tensions and convinces one that precipitate use of positive pressure is unwarranted. This is based largely on the reasoning that cavities become closed by concentric contraction of their walls. The conception that cavities become bridged over and obliterated by having their walls approximated is dismissed with the statement that this has never been proved. The play of forces which permits collapse of the lung, the ease or difficulty with which various types of lesions may be affected, and the mechanisms of healing are discussed in excellent and orderly manner.

Aside from pneumothorax, the action of which is a pattern to be imitated by other measures, specific consideration is given phrenic nerve paralysis, scalenotomy, alcohol injection of the intercostal nerves and apicolysis with paraffin plombage. Each, alone or in combination, is recognized to have a

limited place Phrenic nerve paralysis has been disappointing in Joly's experience and its results are uncertain, it has the disadvantages of disabling healthy parts of the lung and adding to the risks of a later thoracoplasty, should this be necessary The most interesting conception presented is that of "hypotensive" thoracoplasty By this is meant limited rib resection to relax selected underlying cavity-bearing lung which then may heal in the natural way Ample time must be allowed before the ribs are permitted to regenerate, and this is accomplished by treating the periosteal beds with ten per cent aqueous formol solution at the time of operation, or in some cases extraperiosteal resection is performed Some good results are demonstrated and one is impressed that the method represents a real advance in certain situations The great advantage and necessity of sanatorium treatment in all cases requiring collapse therapy are stressed Joly effectively destroys the idea that collapse therapy is a standard method for mass treatment of tuberculosis and establishes advanced conceptions on the basis of which thoughtful and logical discrimination can be applied in each case

**BENJAMIN GOLDBERG** *Clinical tuberculosis Edited by Benjamin Goldberg with the collaboration of 33 contributors Volumes 2, pagged in sections comprising altogether pp 1550, with 640 half-tone and line engravings and 9 full-page colored plates, Philadelphia, F A Davis Company, 1935, fabrikoid, \$22 00*

By **EMIL BOGEN**

The two volume encyclopedia of clinical tuberculosis produced by Doctor Goldberg and his thirty-three collaborators constitutes one of the most stimulating presentations of modern tuberculosis lore that has appeared for a long time Almost each contributor manages to put in the course of his chapter some new conception or revolutionary assertion to startle the reader from too ready acceptance This radical espousal of unproven innovations is both refreshing and appealing, but it is, perhaps, fortunate that its high price will tend to prevent it from falling into the hands of general practitioners and novices in tuberculosis who might too readily accept its provocative assertions for gospel truth

The binding and arrangement are excellent, the typography and illustrations clear and attractive, and the index comprehensive, but typographical errors are present, the roentgenograms appear indiscriminately as positives and as negatives, and there is no table or index to the numerous reproductions Excellent bibliographies are appended to some chapters, but others are scant or completely absent Most of the contributors hail from Chicago, a few from New York and Pennsylvania, and one from Colorado Space forbids adequate discussion of each of the moot questions brought up in the forty-eight chapters

of this work, or even a full appraisal of the exceptionally fine presentations encountered in certain chapters, but a few of them might be mentioned

A wealth of authoritative data and judicious interpretation of the available statistics bearing on the epidemiology of tuberculosis opens the book. The stress on inherited resistance in the children of tuberculous subjects appears a rather questionable explanation, however, for the mechanism of a well demonstrated phenomenon

The elaborate life cycle described for the tubercle bacillus, with streptococci, diphtheroids and even enteric organisms appearing as disguises assumed by the elusive changeling, remains a strictly personal exposition of views still generally rejected. The chemistry and cultural characteristics of the classical acid-fast rod are given scant attention, and the changes in the differential blood count in infected animals and humans which Schilling, Sabin, Medlar and others have so strongly stressed is not even mentioned

Considerable differences of opinion are expressed in different chapters regarding the validity of the Ranke schema for the pathogenesis of tuberculosis, the primary localization, secondary generalization and tertiary isolation admired by the pathologist being replaced with a primary dissemination, and secondary localization with only intermittent and accidental later spreads in the clinical description of haematogenous tuberculosis

The appealing and plausible conceptions of Coryllos of the pathogenesis of cavitation in tuberculosis are presented by the author with a wealth of citation of physiological facts, pathological inferences, and surgical recommendations. It is sad that the pathologist and the other surgeons writing in this group maintain an ominous silence on this subject. The qualitative classification of tuberculosis presented by Ornstein and Ulmar with a profusion of illustrative clinical case reports receives more consideration, both critical and enthusiastic, from their colleagues

The rôle of allergy in tuberculosis receives a highly varied treatment in different chapters, scouted by the pathologist, stressed by the clinicians, endorsed by the immunologist and feared by the pediatrician, its highly debatable position is apparent. The differences of opinion expressed on the therapeutic value of tuberculins or the prophylactic value of BCG by different contributors are accordingly quite understandable

The cited increase in the alkali reserve in tuberculosis, contrary to the finding of most workers, and the recommendation of a holder for cigars and cigarettes, with the consequent smoking further into the stump which this allows, may be questioned. Special diets seem to have proven their worth in intestinal and in skin tuberculosis, but controlled studies to support the elaborate regimen proposed are still needed. Congenital cystic disease of the lungs is ignored both in the differential diagnosis of tuberculosis and in the aetiology of idiopathic pneumothorax.

Among the chapters on *Extrapulmonary Tuberculosis*, the treatment of laryngeal tuberculosis is particularly complete, especially in its bibliography. Among the newer procedures recommended in tuberculous patients where surgery may be contemplated are bronchoscopy, electrocardiography and intravenous urography. The treatment of diabetes in the tuberculous is fully discussed, but an interrelationship between the diseases is viewed critically.

The extensive experience of the Matsons with artificial pneumothorax and the more conservative measures in collapse therapy is admirably presented, with abundant citation of cases and of statistical data. Followers of Alexander may wish that the temporary phrenic operation were given more consideration, and that intercostal neurectomy might at least be mentioned. The confidence and optimism with which partial and complete thoracoplasties are recommended makes one wonder at the complete omission of any reference to the Adams-Vorwald operation of bronchial occlusion, or to lobectomy or pneumectomy which have been suggested in certain cases.

The two chapters on *Physical Diagnosis* are divided, for no obvious reason, and contain repetitions suggesting the refurbishing of older articles for this volume without adequate scissors and blue-pencilling. The subjective sensory reflex symptoms of Pottenger are quoted at considerable length, but no mention is made of the objective signs of muscle spasm and atrophy described by the same author.

The chapter on *Prophylaxis* emphasizes the contagiousness of tuberculosis, in strange contrast to the following chapter on *Home Treatment* by the same author, in which the very possibility of adequate institutionalization of all open cases is scouted. Home treatment, strange to say, is advised especially for the wealthy, who are apt to be best able and willing to profit from sanatorium care.

The discussion of *Medicinal, Symptomatic and Tuberculin Therapy* emphasizes the value of calcium and vitamin D, which still require verification, and omits mention of vitamin C, which is probably of more importance, at least in intestinal cases. The treatment of pulmonary haemorrhage with morphine, emetine and coagulants may be questioned. Tuberculin therapy is described only to be condemned in this chapter, and the chapter entitled *Tuberculin* is concerned only with its diagnostic application.

Although conservative and somewhat apologetic, the chapter on *Climate* insists on its value and suggests possible extensions of its use. No consideration is given to the possibilities of air-conditioning in securing desired climatic conditions.

Controversial matters abound in this publication, but it is just in this that its chief merit may be found to lie. No other book in recent years has been so replete with stimuli for further investigations and of suggestions as to the direction in which future work is indicated. Without accepting Doctor Gold-

berg's pessimistic avowal that tuberculosis will continue to rank as one of the outstanding scourges until a specific remedy for the disease is discovered, we may recognize the importance of research in accelerating the decline that has occurred. If but a few of the problems for which he and his collaborators have so boldly presented tentative answers may be solved within the near future as a result of work stimulated by this daring sally, we may well be grateful for the labors which it represents.

A. CALMETTE *L'infection Bacillaire et la Tuberculose chez l'homme et chez les Animaux. Étude Biologique et Expérimentale. Vaccination Préventive*, 4th edition entirely revised and completed by A. Boquet and L. Nègre. With 33 plates and 51 illustrations in the text, pp. viii + 1024, Paris, Masson et Cie, 1936, cloth, 175 francs.

By MAX PINNER

Professor Calmette's textbook needs no introduction to the readers of the *Review*. Undoubtedly most of them are familiar with previous editions or with the English translation. Anyone who is actively interested in the fundamentals of phthisiology has consulted this standard work. It has always been an unfailing aid for basic information. The information it offers is in many regards considerably different from the current teaching in this country. But the important thing is that it is the book of *one* man, of a true scientist with a wealth of first-hand information, a book decidedly written with a pen and not with scissors as is so often the case with textbooks. It would be quite futile, therefore, to point out differences in French and American teachings, to enter into controversies. A valid refutation could not be undertaken on a smaller scale than that of the book, and this would be an appalling task.

One of the great values of Professor Calmette's text is the fact that it is a complete and logical exposition of the French teachings. It is for us *the* authoritative statement of all those topics on which disagreement exists between the two countries, such as portal of entry, filterable virus, BCG, to mention only the outstanding ones.

The fourth edition, prepared by Doctors A. Boquet and L. Nègre, is a worthy successor to the last edition of 1926. The editors have digested a tremendous amount of work that appeared during the last decade, and they have added it to their master's text, truly *avec le sentiment de remplir un pieux devoir envers la mémoire de notre Maître*. The two editors, both famous in tuberculosis research, have completely modernized the book without detracting from its unity. This is probably the highest praise possible for such self-effacing work.

To return once more to the difference of opinions, any worker in tuberculosis may disagree with many of the tenets expressed by Calmette, Boquet, Nègre, but none can afford not to know them.

JOHN B HAWES, 2ND, AND MOSES J STONE *The diagnosis and treatment of pulmonary tuberculosis With a foreword by Richard C Cabot With 43 illustrations, pp 211, Lea & Febiger, Philadelphia, 1936, cloth, \$2 75*

By CHARLES W MILLS

In their preface the authors say that their purpose is to bring up to date a book of twenty years ago by one of them on the same subject—a book then characterized by Dr R C Cabot as short but authoritative They state their belief that there is need for such a book They have fulfilled their purpose in all of these particulars, for the present book is condensed, authoritative, up-to-date and timely

A brief summary will indicate the book's scope and arrangement A short historical chapter is followed in order by chapters on *History Taking, Symptomatology, Physical Examination, Differential Diagnosis, Tuberculosis in Childhood, Roentgen-ray Diagnosis, Laboratory Methods, Sanatorium and Home Treatment, Treatment of Symptoms and Complications, Collapse and Compression Therapy, Heliotherapy, Climate, Specific Treatment by Serums, Vaccines and Drugs, and Diet* These chapters very expertly cover what may be considered subjects fundamental to any general book, however brief, on tuberculosis Then follow a few chapters on what might be called odds and ends,—*Rehabilitation*, dealing with occupational therapy and farm colonies, the *Heart in Pulmonary Tuberculosis, Tuberculosis in the Aged, Marriage and Pregnancy, and Dangerous Trades* Of course such odds and ends of so large a subject could be indefinitely added to, but the above comprise the authors' selection of those which they consider important enough to include They state in their preface that they have purposely omitted, as out of place in a simple textbook of this sort, such intricate subjects as immunity, resistance, allergy, etc There is finally a chapter on the *Prevention of Tuberculosis*, dealing with public health aspects

At the end of each chapter is a concise summary of the contents and a bibliography which is called "Suggestions for Supplementary Reading" Both of these features are well done and helpful There are 43 illustrations, most of them from X-ray films, well reproduced

The chapters on *History Taking* and *Physical Examination* contain many helpful and practical hints In those on diagnosis, an excellent balance is kept as to the value of the various methods, and the need of their proper coordination is maintained The great importance of roentgenology is stressed but extremists please note these sentences "Some roentgenologists are of the opinion that the acuteness of the infection and the activity of the lesion may be judged by the roentgen-ray plate We feel that although a careful study of the film may help in determining a decision as to this, this important question should in the main be based on clinical signs and symptoms" The

chapters on treatment also show a due sense of proportion. Those on collapse therapy, a hard subject to condense, are excellent.

There is an uncommon lot of good practical common sense throughout. Essentials are stressed and unnecessary frills avoided. One or two illustrations will serve to illustrate this. For instance, "in many cases of bronchiectasis the diagnosis is clear, so that the use of lipiodol, at best a disagreeable procedure and not entirely devoid of risk, may well be omitted." That this advice is given in the interest of the patient and not in advocacy of any lack of thoroughness the sentence immediately following in the text makes clear. "Repeated examinations of the sputum by concentration methods and repeated roentgen-rays taken before and after postural drainage will help." And again, "Do not waste time over nonessentials. Much time has been wasted, for instance, in percussing out the narrow strip of normal resonance known as Kroenig's isthmus. From this certain things were deduced and usually wrongly. Likewise before the development of roentgen-ray technique, it was considered necessary to percuss out the excursion of the bases behind. At present with roentgen-ray, and especially fluoroscopic examination available in almost every instance this is a waste of time and energy." Surely this is good "horse sense." On the other hand, in the same connection exception might be taken to the following statement a few pages later. "*Do not* look at the roentgen-ray film or read a roentgen-ray report of the lungs until you have finished your own clinical examination of the chest and have recorded your findings." This is excellent advice if meant for the medical student or for the practitioner endeavoring to perfect his technique of physical examination and for such also percussion of Kroenig's isthmus or of the basal excursion may be a valuable exercise. But to the trained and busy examiner it would seem just as logical and on many occasions less time-consuming to check up his X-ray findings by his physical examination as *vice versa*. However, there are very few statements in the book that anyone acquainted with tuberculosis work could take exception to. The authors are not extremists in any sense and there is an admirable absence of radical or arbitrary views. Perhaps there is a tinge of the latter in this, however. "If by the time you examine the patient the sputum is positive someone is to blame," (either patient or previous physician). This may be an ideal for the future when public health control is so extended or the populace so educated that every individual as a matter of course is periodically examined, but the statement seems a little strong when applied to conditions at present. But for one such sentence a hundred others might be quoted to show the balance and good sense of the book.

The medical student, the general practitioner or the tuberculosis specialist who wishes a short, authoritative and common sense presentation of present views on the clinical aspects of pulmonary tuberculosis will find it in this book.

A short introduction by Dr R C Cabot ends with the following words in which I heartily concur "Altogether I believe Dr Hawes and Dr Stone have given the general practitioner exactly what he needs, a concise, sensible, expert book on a subject of great importance"

FELICE PARODI *Il Pneumotorace Contralaterale primario di Maurizio Ascoli*  
Pp 225, A Wassermann, Milano, Italy, paper, 30 lire

By GEORGE W WEBER

For a quarter of a century Maurizio Ascoli has been the inspired high priest of the principle of hypotension in collapse therapy. He first began to advocate and practice it in 1912 when he proposed simultaneous bilateral pneumothorax at low pressures, thus opening a new era in the practice of pulmonary collapse. Since 1929 he has gone still further by applying pneumothorax to the contralateral healthy lung in those cases in which a pleural symphysis prevents collapse of the diseased side, calling this new procedure "primary contralateral pneumothorax". His reasoning is as follows. During the course of a usual pneumothorax, the contralateral lung, if already infected, very often shows decided improvement and even complete recovery. He rejects, as being contradictory to the basic idea of pneumothorax, Forlanini's explanation that this might be due to vicarious increase of activity. In his opinion, the improvement takes place only because the contralateral lung is reduced in volume, as demonstrated by Epifanio, and consequently becomes functionally less active. Furthermore, the modifications of the intrapleural pressures of one side are also transmitted to the other side. Parodi, Bordet and others had already found this to be true in unilateral and bilateral pneumothorax. Ascoli, on these premises, considers the lungs in the pleural cavities not as two separate organs, independent from each other, but as one unit which reacts uniformly as a whole to any change of pressure exerted upon one of its sides. In other words, the pneumothorax he proposes will release the elastic tension and reduce the functional activity of the contralateral lung in the same way, although in a lesser and variable degree, according to the mobility of the mediastinum, that it releases the elastic tension and reduces the functional activity of the homolateral lung. The only elements necessary for its success are an entirely free pleural space on the good side and a fairly movable mediastinum. Its management is the same as that of a homolateral hypotensive pneumothorax. The final pressures must produce a bilateral release of tension with a corresponding decrease of functional activity, which will be at the expense of the air reserve, without eliciting at the same time vicarious compensatory reactions. The "threshold of pressure" should be between the extremes of  $-4$   $+2$  in expiration.

Parodi's understanding of the mechanism of action of such pneumothorax



is quite at variance with Ascoli's. His contention is that the mechanical actions and reactions induced by collapsing one lung are transmitted to the other lung not through the mediastinum, but by the variations of tension which, as a result, take place in the bronchial trees. Unfortunately, it is not possible in this short review to go into the details of his theory, which, though interesting and plausible in parts, is, in my opinion, vitiated by the excessive importance he attributes to the weight of the lung in the production of intrapulmonary tension. Consequently, his judgment is also biased when he states that the deviation of the mediastinum, being the result and not the cause of the hypotension produced in the uncollapsed lung, which is true, is not essential to the ends of the treatment. Yet, how can an effective hypotension take place unless some tissues give way? The bronchial relaxation seems hardly sufficient.

Another major point of disagreement between the two authors is the volumetric change in the uncollapsed lung. While Ascoli maintains that its volume decreases, the contrary is believed by Parodi. In his opinion, the uncollapsed lung undergoes greater expansion the moment that the resistances to its distension by the opposite lung are abolished when the latter is collapsed.

It is evident that Parodi's conception is more complex and, perhaps for this same reason, less clear and convincing. However, the discrepancies are more theoretical than practical and they cannot involve such differences in technique as Parodi seems to believe. Pleural pressures and pleural gaseous interchanges being what they are, no lung could be kept within definite and narrow limits of collapse for any length of time. Of importance is the fact that they agree on the basic principle of hypotension.

Needless to say, the application of the primary contralateral pneumothorax is one of necessity and not of choice. First devised to treat unilateral lesions only, its indications have lately been extended to include bilateral lesions, in which case the pneumothorax is applied to the less diseased lung, always provided that the pleural space of the more diseased one is obliterated. It may also be used to render more effective other surgical procedures such as phrenic interruptions and partial thoracoplasties. The lesions which will best benefit from it are of the exudative or fibrocaseous type with tendency to retraction, located in the upper portion of the upper lobes.

This additional indication of pneumothorax therapy proposed by Ascoli is based upon sound principles, but whether it will be accepted and widely applied is doubtful. The idea that hypotension is sufficient to create in the lung conditions apt to stimulate the reparative processes of tuberculous lesions is still too foreign to many. It may be expected, therefore, that primary contralateral pneumothorax will have, like its older brother, the simultaneous bilateral pneumothorax, to overcome a good deal of scepticism and opposition before being allowed to join the ever increasing family of collapse therapy.

PR HOVELACQUE, OLIVIER MONOD, AND HENRI EVRARD *Le thorax, anatomie médico-chirurgicale With 125 plates and diagrams designed by A Moreaux, pp 356, Paris, Librairie Maloine, 1937, paper*

By ADRIAN A EHLE

Almost inevitably one approaches each new anatomy book with mixed feelings of reverence and weariness engendered by a lack of expectation. Many years have cast a hallowed adumbration on the subject. Seemingly the facts remain static and the efforts of successive authors are directed to a reexposition of these facts. In general this book has turned rearranged lights upon the anatomy of the thorax, bringing into sharper focus some points and allowing others to remain in the penumbral zone. By title and by intent (as expounded in a modest introduction) the authors have written an anatomy book to provide the thoracic surgeon and internist with a satisfactory and rather meticulous view of the region in which they work.

Foremost in the minds of the authors is the thought of the development and expansion of thoracic surgery. With this in mind they have presented the surgeon with a book that brings into the light the practical and useful knowledge of the thorax and its contents. Naturally with this in view some anatomical points have been treated rather slightly. Hence, because of its importance in surgery, the phrenic nerve, its abnormalities, and its variations, have been thoroughly and lucidly described in six pages supported by excellent drawings. On the other hand the vagus nerve has been rather summarily dismissed. But there can be no quarrel with that shift of focus.

In a conventional fashion the authors have divided the book into four parts. The first is devoted to the descriptive anatomy of the thoracic wall. Even in this basic section the emphasis has been placed on answers to the question, "But how does this anatomy affect the course of disease or one's surgical efforts?" To provide a satisfactory answer the authors have stressed the importance of these structures in regard to their thoracic relations. Thus one finds the *latissimus dorsi* and *serratus magnus* muscles described as accessory muscles of respiration. It is assumed that the persons who will find this book useful will already have acquired a fundamental knowledge of anatomy.

In the second section there is the descriptive anatomy of organs contained in the thorax. Particularly satisfying is the description of the intrapulmonary ramifications of the bronchi—a controversial subject on which several views have been presented. The remaining organs are described with uniform excellence.

The third and fourth sections contain the topographical anatomy of the thoracic wall and contents respectively. In preparing these sections the authors have dissected many cadavers and have also made full use of clinical examination of living patients and roentgenograms. The result is a clear

projection of the thorax. Because the book has been written for the surgeon and internist there is much in it that has been slurred or skipped entirely in the older anatomies. The anatomy of the pleural dome with its suspensory apparatus of connective tissue, ligaments, and aponeurotic attachments, is outlined in a lucid fashion. There is a very good description of the mediastinum and the triangular ligaments. In describing the pulmonary pedicles the authors have chosen to peer at anatomy between the blades of retractors. However, this is not a book of operative surgery nor is it a conventional surgical anatomy. (The authors have in preparation a volume of truly surgical anatomy.) In this volume anatomy is not described as it appears through classical operative incisions.

It is too bad that the credit given to other authors is so superficial. There is no bibliography, many apparent authorities are cited by parenthetical inclusion of their names without mention of when their work was done or where it may be found.

The format and typography of the book are worthy of compliment. There are also excellent illustrative drawings and diagrams. In short, the book is a commendable presentation of thoracic anatomy, it is meant to be, and should prove to be, useful to the practitioner in thoracic medicine and surgery. Even considered as anatomy, unadulterated by the practical, it compares most favorably with the many volumes that have passed through numerous editions and revisions.

A. L. PUNCH AND F. A. KNOTT *Modern treatment of diseases of the respiratory system. With 96 plates and 31 figures in the text, pp viii, + 289, P. Blakiston's Son & Co., Inc., Philadelphia, 1936, cloth, \$5.00*

By FREDERICK BECK

Although written principally for the general practitioner and the senior medical student, this book is nevertheless a brief and valuable guide for the internist treating respiratory diseases.

The subject matter treated ranges from the milder forms of respiratory diseases, such as the common cold and other acute upper respiratory infections, through the diseases of the lungs, bronchi, and pleura, including bronchiectasis, bronchial asthma, the pneumonias, abscesses, tuberculosis and tumors. The differential diagnosis, symptomatology and treatment of these conditions are briefly discussed. Diagnostic and therapeutic procedures such as the injection of iodized oil into the bronchial tree, aspiration of fluid from the pleural cavity, pleural lavage, blood transfusion, pneumococcus typing, and artificial pneumothorax are completely described and discussed as regards their techniques and indications, and are well amplified by diagrams. The discussions concerning the diagnosis, management and therapy of bronchiectasis, pul-

monary neoplasms and tuberculosis of the lungs are particularly outstanding and complete in regard to present methods of treatment. The reproductions of the roentgenograms to illustrate these conditions are excellent.

While the authors must be dogmatic in such a brief treatise, their views are predominantly conservative and sound. Their faith, however, in the prophylactic use of vaccines in upper respiratory infections and in the pneumonias is probably too enthusiastic.

It is unfortunate that the briefness of the book precluded the inclusion of a bibliography as a supplement to the text, but it is nevertheless a concise and thorough guide to a rational method of the management of respiratory diseases.

EMILIANO ELZAGUIRRE *La Primo-Infeccion Tuberculosa* Pp 380, *Liberia International, San Sebastian, 1934, cloth*

By FRIEDRICH G. KAUTZ

The author, who previously contributed to the Spanish medical literature valuable books concerning pulmonary surgery and a general book on pulmonary tuberculosis, presents in the present monograph the results of a comprehensive study of two hundred cases of primary tuberculosis of the lung. The cases came under his observation in the course of three years at the Tuberculosis Hospital and Dispensary of San Sebastian. With the contributory work of a large staff of coworkers and pupils the author's book is devoted to all the problems which arise from an anatomical and clinical viewpoint. They are treated in a broad and ample manner with a critical analysis of the modern concepts of the world literature. In the first introductory chapters the questions of epidemiology, heredity, contact and their medical and social importance, chiefly in relation to the incidence and fatality of pulmonary tuberculosis in Spain, are discussed. The author outlines the difficulties of an early and exact diagnosis and therefore emphasizes the necessity of a close collaboration between the phthisiologist and the pediatrician and the family physician. Short chapters providing necessary and clear-cut outlines of the fundamental problems of phthisiology are masterpieces of conciseness. A large part of the volume is devoted to the primary infection and its intrathoracic lymphatic reactions. The author describes his concept of the occurrence and development of primary tuberculosis, he emphasizes the necessity not to refer in the question of the evolution of an areated pulmonary lesion to the results following the injection of large doses of tubercle bacilli in animal experiments. The development and course of a primary focus which have occasionally been observed in children show that the alveolar lesion and the consecutive tissue and lymphatic reactions are different from animal experiments they may be misleading in their application to human pathology. If there is any similarity in the course of the reactions this can be shown experi-

mentally with a small dose of not more than 0.01 mgm. These basic observations of the tissue reaction allow conclusions as to the period of incubation, of the primary course and eventually of a prognosis. The clinical discussion is devoted to the various localizations and is aided by many informative illustrations. Later chapters describe the lymphatic reaction, and here the author presents anatomical postmortem findings. Finishing with the outlining of the clinical syndrome of the primary infection and its regression, the author passes over to the secondary manifestations, describing the diagnostic value of the cutaneous tests, of the eruptive skin lesions and their differential diagnostic distinction, and of the primary phthisis with and without miliary tuberculosis. In brief chapters the prevalent problems of therapeutic procedures are dealt with, complemented by interesting statistics concerning the prophylaxis with BCG. The material offered also many occasions to observe the complications involving the pleura and the pericardium, and the lesions were studied in relation to their lymphogenic origin. These conditions are further explained in an ample manner by X-ray pictures and anatomical drawings. The book is an elaborate piece of research work based on a relatively small material, the intensive study of the cases, their critical examination and the habit of the author to refer to the most modern concept concerning the problems at hand, make this monograph a work of high standard.

AGOSTINO CURTI *Le Lobiti Tisiogene* Pp vi + 130, Milano, Tipografia Enrico Zerboni, January 20, 1934, paper

By FRIEDRICH G. KAUTZ

According to Bernard a tuberculous lobitis (lobar tuberculosis) is the involvement of at least one whole lobe. The rich material of the Ospedale Sanatoriale in Vialba offered the opportunity to select over one hundred cases which presented the clinical and roentgenological appearance of lobar tuberculosis. In brief chapters the anatomical and aetiological foundations are discussed. As compared with the relative age at the onset of pulmonary tuberculosis in general in the adult, there is a marked increase in frequency between the ages of 21 and 30 years in the development of lobar involvement. This age-group represents nearly 50 per cent of all the cases. While the involvement of the right upper lobe is by far the most frequent, the left upper lobe is affected only exceptionally. Of 106 cases of tuberculous lobitis there were 101 in the right upper lobe, only one in the left side, and four cases were in the right middle lobe. The average frequency of left-sided lesion differs somewhat from previous statistics in the literature amounting to 3.5 per cent. The chapter on the pathogenesis maps out the aetiological importance of inhalation, of endogenous reinfection by the bronchi and the hilar lymph nodes. This latter source of infection is represented by simple and hyperplastic hilar lymph-

adenitis and leads, by the way of ganglio-pulmonary or interlobar ganglio-bilar propagation, to interlobar and peri-interlobar tuberculous lesions. The chapter closes with a brief outline of haematogenous spread and with interesting remarks on the influence of anatomical-functional considerations. Many pages and illustrations are devoted to the radiological and clinical appearance which are supplemented by short clinical reports of 106 cases. Diagnosis, prognosis, and therapy and their results, including collapse therapy, are described. The author gives adequate and somewhat more detailed information about the fate of the patients during a period of one year and more following the beginning of the treatment. Many schematic and roentgenological illustrations explain the text. The make-up of the book is indicative of the high level of modern Italian scientific literature.

ED WERDENBERG *Beurteilung und Behandlung der Augentuberkulose. Beilageft zu Monatsblätter für Augenheilkunde, vol 95, Ferdinand Enke, Stuttgart, Germany, 1935*

By HERMAN ELWYN

Werdenberg begins his discussion by tracing the development of our knowledge of tuberculosis of the eye. He outlines four stages (1) a pathologico-anatomical stage, beginning with v. Michel, (2) a stage of experimental investigation, beginning with Cohnheim, (3) a stage of investigation into the primary focus of tuberculosis, based on the work of Axenfeld and de la Camp, and (4) a stage based on the fundamental work of Ranke, in which there has evolved our understanding of the relation of tuberculosis of the eye to the general tuberculosis infection of the body. The various phases in the course of tuberculosis correspond to the three stages of development according to Ranke.

Although the manifestations of ocular tuberculosis belong to Ranke's secondary stage, that of general dissemination, they show, nevertheless, early secondary, secondary, and late secondary forms. The type more closely related to Ranke's primary stage, with its normal reaction of the organism toward tuberculosis infection, is the early nodular tuberculosis of the iris, a juvenile form of tuberculosis. The type occurring in the secondary, hypersensitive period, is the diffuse plastic exudative iritis of puberty and the postpuberty period. Corresponding to the tertiary, partially immune, period, is the late secondary productive fibrous tuberculosis, occurring especially in advancing years. A special place in the scheme of tuberculous infection must be given to the juvenile retinal periphlebitis, the haemorrhagic form of ocular tuberculosis.

Clinically, the diagnosis and treatment of tuberculosis of the eye is dependent upon a proper understanding (1) of the characteristics of the various forms of tuberculosis of the eye, (2) of the intrathoracic source of infection, and (3) of the general tuberculous infection of the body.

Werdenberg finds three main forms, the exudative, the productive and the fibrous. When the several forms occur together, one usually predominates. The exudative is the more malignant "toxin-sensitive" form. The productive and fibrous are the less sensitive and more benign forms. This distinction also influences the specific treatment, tuberculin being indicated in the productive and fibrous forms and contraindicated in the exudative form.

There is a certain antagonism between ocular tuberculosis and intrathoracic tuberculosis. Werdenberg calls this a normal antagonism when there is severe ocular tuberculosis with slight intrathoracic findings. In 500 cases in which roentgen films of the lungs were studied this normal antagonism was found in 60 per cent. As an inverse antagonism Werdenberg characterizes the presence of a mild tuberculosis of the eye with severe pulmonary tuberculosis. This he found in 10 per cent.

Toxic symptoms of general tuberculous infection are more frequently observed in the exudative than in the proliferative and fibrous forms, but frequently there is no relationship between the particular form and the toxic symptoms. Treatment must also take into consideration the general infection.

The diagnosis of tuberculosis of the eye is, strictly speaking, a probability diagnosis, depending upon the clinical picture in association with the physical and roentgenological examination of the chest. A positive tuberculin test helps, but a negative test does not necessarily exclude it.

The treatment of tuberculosis of the eye is general and local, and has three points of attack: (1) the organism as a whole, (2) the tuberculous focus in the body, and (3) the eye. Treatment of the organism as a whole is a constitutional one and involves an attempt to change the immunobiological reaction of the organism to the infection (*Umstimmung*). This is accomplished by climatic treatment and by means of tuberculin. The latter involves strict indication for its application and proper dosage. It should not be schematic but according to the individual need. Werdenberg uses Sahli's subepidermal method. He divides the tuberculins according to their toxicity: (1) slight toxicity, Rosenbach's sensitized bacillary emulsion, (2) immunizing action with moderate toxicity, Koch's bacillary emulsion, Béranek, Tebeprotein, (3) toxic action, Old Tuberculins, A T O, A T, the latter is the most toxic.

In the final chapter, Werdenberg gives his statistical results. He has treated 1,100 cases of ocular tuberculosis. Of these the uveal tract was involved in 85 per cent of the cases, with iridocyclitis in 65 per cent and choroiditis in 20 per cent. Puberty and climacterium are the most frequent periods of life for the occurrence of ocular tuberculosis.

The 33 page pamphlet presents a short and concise review of the present conception of tuberculosis of the eye by one who has had a large experience. It is, perhaps, too short and too summary, but it is well worth a closer scrutiny.

CHARLES LE SÉAC'H *L'Image granitée post-hémoptyique (Etude clinique et pathogénique)* With 13 figures in the text, pp 141, Librairie Louis Arnette, Paris, 1936, paper

By J BURNS AMBERSON, JR

The subject of this monograph has to do with the finely mottled or studded, hence "granitic," appearance of the roentgenograph of the lungs of a tuberculous patient after he has had one or more haemoptyses "Granitic" is a good descriptive term, indicating a grainy or granular type of shadows All are familiar with the picture which may represent an acute posthaemorrhagic development going on to caseous pneumonia, resolving almost completely or leaving behind the small round densities which persist indefinitely or undergo fibrous transformation In this country the shadows are usually taken to represent a dissemination of tuberculous lesions from the aspiration of blood laden with tubercle bacilli, though a few have explained them on the basis of atelectasis Séac'h considers in detail the clinical and experimental evidence presented by Austrian and Willis and the reviewer in the early 1920's, and argues that the conclusions were wrong that the changes are specifically due to bacillary infection Likewise, he opposes the atelectasis theory His conclusion is that the shadows represent exudation in the lung and that this is caused by the same thing as the haemorrhage, namely, a disturbance of the "neurovegetative equilibrium" An interesting discussion draws attention to the nervous regulation of pulmonary function, an important mechanism barely known to most of us Nevertheless, the author is not able to adduce much objective evidence for his hypothesis, and leaves it as such More recent American work has provided strong evidence from clinical and postmortem examination that the former interpretation of these shadows is the correct one Incidentally the book includes a careful analysis of the clinical features of haemoptyses An unusual literary feature is the dedication Thirty-seven persons are specifically named for this honor, besides numerous others included in groups

ETIENNE BERTHET *Rôle des Voies Lymphatiques dans la Génèse de la Tuberculose Pulmonaire, leurs rapports avec la tuberculose pulmonaire interstitielle* With a preface by Professor Sergent With 12 illustrations, pp xii + 98, Paris, G Doin & Cie, 1936, paper, 20 fr

By MAX PINNER

The apparent and real puzzles presented by the pathogenesis and epidemiology of tuberculosis stimulate once in a while an attempt at a revolution against what appears to be well established fundamentals The present monograph



is such a revolution, or probably more correctly a revolt, since the scope of the attack is rather slender in comparison with the broad basis that is assailed. The argumentation proceeds in orderly and logical fashion step by step, but the basis of each step seems narrow and tenuous.

It is well worth while to follow Doctor Berthet through his reasoning, step by step, armed with all the critical reserve that the importance of his subject deserves. Doctor Berthet first states that the primary complex as elaborated by Parrot, Kuss, Ghon, Ranke is not a reliable indicator for the portal of entrance of tubercle bacilli. First, because according to Calmette bacilli cannot reach the lower air-passages with the inspired air under physiological conditions, this is deemed satisfactorily proven by the fact that the alveolar air is always found to be sterile. But since coal and siliceous dust find apparently easy access to the pulmonary parenchyma it needs probably more than an authoritative citation to settle this question. Secondly, it is stated that the anatomical and histological characteristics of the primary complex do not permit of a distinction from other, that is, reinfection foci. This argument appears inviting only by virtue of the totally inadequate description that is presented of the primary complex, it is deplorable that Doctor Berthet does not mention in this connection the fundamentally important work of such authors as Schurmann and Blacklock, but only casuistic reports of apparently absent or atypical primaries. While negative findings *per se* are less convincing than positive ones, it should at least be demanded that negative results be based on equally painstaking search as those that yielded positive results. For this reason, all merely clinical and roentgenological reports of absent primary foci attest only to the inferiority of the methods employed. Doctor Berthet puts much weight on the well known fact that pulmonary lesions may be produced by bacilli deposited anywhere within the body, but it still has to be shown that by any other than local administration, a focal pulmonary lesion with the characteristics of a primary complex can be induced.

The next chapter reopens the old discussion of anastomoses between the cervical and mediastinal lymphatic chains. Since it is admitted that such anastomoses exist, if at all, only in exceptional cases under normal conditions, emphasis is put on the clinical necessity of assuming such connections following inflammatory alterations. However, every pathologist has seen cases in which both lymphatic systems were involved by tuberculosis. It is, then, always found that in terms of massiveness of involvement, the two systems form two pyramids, the cervical with a superior, the mediastinal with an inferior broad base, and the apices of the pyramids meeting somewhere near the borderline of the two regions. This is an impressive and convincing argument for the independence of these two regions of lymphatic drainage.

The frequency of tonsillar involvement, presented as argument for the assumption that tubercle bacilli enter frequently through these organs, is no

criterion, since practically all, if not all, reports cited are based on the examination of biopsy specimens without any evidence that the tonsillar lesions were the only, or at least, the apparently oldest foci

For similar reasons, the clinical reconstruction of cutaneous primary infection from the neck—made invitingly possible by actual or assumed impetiginous lesions—cannot be given serious weight

A group of 14 patients is presented with calcified cervical lymph nodes and homolateral pulmonary tuberculosis in support of the author's view of direct lymphatic drainage from the cervical region into the pulmonary parenchyma. Since Doctor Berthet declines to accept the pathologico-anatomical evidence for the reconstruction of a chain of developments, the same criticism ought to be applied to roentgenological evidence

Doctor Berthet concludes that a frequent mode of primary infection is through the upper respiratory organs and the skin of the neck, that, at least under pathological conditions, lymphatic drainage from the cervical to the mediastinal lymph nodes and hence to the pulmonary parenchyma occurs, that direct aerogenous infection of pulmonary tissue is impossible, and that bacilli entering through lymphatic tissue are so deprived of their virulence that, reaching the lung, they produce benign, interstitial lesions. We are not told, however, how those bacilli enter the lung that cause rapidly destructive phthisis

It was not necessary in the reviewer's opinion to prove again that tubercle bacilli may enter the lung by other but the aerogeneous route, we are all agreed on that. In support of the author's contention, it was necessary to prove that bacilli entering through the portals favored by him, can produce a lesion in the lung resembling a primary complex. This proof has not been attempted

Doctor Berthet's monograph is an interesting and somewhat impatient and breathless study, it is based more on selected literature and circumstantial evidence than on direct observation. It seems, therefore, unconvincing, probably even to those readers who need not plead as definite a preconceived bias as this reviewer

D. B. CRUICKSHANK *Tuberculosis, cancer and zinc, an hypothesis. With an introduction by Sir Pendrill Varrier-Jones. With 26 tables, pp. xv + 75, London, Medical Publications, Ltd., 1936, cloth, 7/6*

By MAX PINNER

If one is confronted with a thesis that promises to explain in a satisfactory manner some of the major problems of the pathogenesis and epidemiology not only of tuberculosis but of cancer as well, if at the same time such a thesis is sufficiently far removed from the well worn (and possibly well tested) ideas

that may sometimes appear stale by familiarity and routine and not too encouraging by their demonstrable achievements, if such a thesis is presented with the unassuming charm of the rather serious causeur and not with the ponderous zeal of the messiah of an epochal thought, then, the reader's aesthetic sensibilities are in danger to be more acutely affected than his critical sensitivity. And so, it is with mellowness, rather than with acuity that one is apt to think of Doctor Cruickshank's book. But this reviewer's mental reaction to the book is totally insignificant lest it be accepted as a broad apology for the evasion of his obvious duty a critical review. Instead he will present in barest outline the chain of thought of Doctor Cruickshank's hypothesis, and hypothesis it is called by its author, and hypothesis appears in large fat print.

The decline in the tuberculosis mortality rate, obviously out of gear with all organized efforts to combat the disease, shows chronologically and quantitatively a close parallelism with the appearance and diffusion of available zinc in human environment (notably by the instrumentality of the zinc-lined milk pail). Further circumstantial evidence, such as the geographical distribution of tuberculosis-resistant animals in zinciferous regions, supports the idea that zinc increases the resistance to tuberculosis.

The sum of the tuberculosis and cancer death-rates has remained constant for long periods, and the reciprocal relation of the two diseases is further suggested by the relative tuberculosis-resistance of cancer-susceptible animals and *vice versa*. While tuberculosis seems to be associated with a hypo-zinc state, the reverse is true of cancer. The combined mortality of tuberculosis and cancer is constantly 20 per cent of the total mortality (in England). The exactly antagonistic statistical behavior of the two diseases can only be explained if it can be shown that the growth of one disease prevents the development of the other. "In the 20 per cent group, who alone are susceptible to those two diseases, the decision as to which disease will ultimately cause death is made at the moment of (or *circum* the moment of) infection by the tubercle bacillus." This statistical postulate is fulfilled by the assumption that the bacteriophage specific for the tubercle bacillus is the virus causing cancer. It is now simple enough as long as the Janus-faced phage is engaged in his battle with the tubercle bacillus, his carcinogenic propensities remain in abeyance, when the battle is won, his neoplastic function is set free.

As far as I can see, Doctor Cruickshank's hypothesis is original. The historical evaluation of bold theorists, like that of bold revolutionaries, is decided by their success. In the absence of material facts it is perilous to attempt a prophesy. But it may be in order to point out the absence of material facts, save some statistical correlations. The statistically assumed influence of zinc on tuberculosis and cancer is unproven, but susceptible to experimental verification. With the incidence of tuberculosis infection which is much higher

than 20 per cent, many a phage-bacillus battle must end in the stale mate of mutual exhaustion, especially since cancer does not appear to be particularly frequent in patients recovered from tuberculosis, this is a point that is not mentioned. The assumption of an antibacterial carcinogenic phage must have originated in Doctor Cruickshank's mind long before Steencken, shortly before the publication of Doctor Cruickshank's book, presented incomplete but suggestive evidence for the occurrence of a tubercle-bacillus phage. If this does exist, its neoplastic qualities must still be shown. Doctor Cruickshank has evaded meticulously and wisely the arguments in the discussion of the infectious nature of cancer.

In brief, it is, generously seen, probably true that, using what Doctor Cruickshank himself calls "diffuse logic," this hypothesis is not contradicted by any known fact *eo ipso*, but it is probably equally true, that none, but rather vague and statistically derived observations, are available at present to support it.

FRED H. HEISE *1000 Questions and answers on T B* *Journal of the Outdoor Life, New York City, 1935, pp vi + 232, cloth, \$ 75*

By CHARLES W. MILLS

The *Journal of the Outdoor Life*, during most of its existence, maintained a Questions and Answers Department. Doctor Heise conducted this department for twenty years and the book under discussion is a selection and compilation from these questions and answers. An attempt has been made to select those questions about tuberculosis which, from the frequency of their appearance, seem to be uppermost in the minds of patients. The questions are classified and arranged under a number of titles and subtitles in an effort to secure sequence and for ease of reference.

The answers are almost without exception excellent. The task of answering such questions must be difficult. Besides a thorough knowledge of the subject, in this case tuberculosis, especially in its bedside aspects, it would appear to require a considerable amount of tact as well as cleverness. A physician answering a question from a patient whom he has never seen, and about whom he knows nothing except for the small amount of information furnished by the question, needs both cleverness and tact if he is to give an answer that will enlighten and satisfy the questioner and at the same time not lead him into harm by attempted self-treatment and not trespass on the proper field of his attending physician. Doctor Heise appears invariably in his answers to have this necessary cleverness and tact. His thorough knowledge of tuberculosis enables him to give sensible and helpful answers and he shows an uncanny ability to avoid pitfalls.

The question-and-answer form is inherently a poorly adapted form in which

to cast subject matter intended for consecutive reading. The effect is necessarily broken and choppy and sustained interest hindered. It must be said, however, that Doctor Heise by means of the sequential arrangement of the questions has succeeded fairly well in overcoming this inherent limitation, and that the book is not uninteresting when read as a consecutive presentation of the subject. Perhaps it is better classified, however, as a very excellent reference book on tuberculosis for patients.

I S FALK *Security against sickness, a study of health insurance, America's next problem in social security*. Pp vi + 423, Garden City, New York, Doubleday Doran and Company, Inc., 1936, cloth, \$4.00

By BERNA RUDOVIC PINNER

This is a comprehensive groundwork for planning a program of health insurance for the United States. The material gathered by the Committee on the Costs of Medical Care is used in the analysis of the situation here, and the marked differences in opinion between members of this Committee, on some issues, of which so much point has been made by interested persons and organizations, are shown to be slight in comparison with their essential agreement. The case for the necessity of a program of health insurance is made out convincingly. The author points out the anomaly of inadequately employed physicians and nurses coexisting with a laity in need of their services. The average individual's expenditure yearly for medical care is well under thirty dollars, but medical care differs from any of the other necessities of life in being unbudgetable. No amount of living-within-one's-means can give one security against an illness, the costs of which may exceed annual income, and when it strikes the breadwinner, may at the same time wipe out the income. In the intervals between depressions, one-third to one-half of all cases of family dependence have their genesis in sickness and its economic sequelae.

Four European systems of insurance against sickness are investigated: the German, the British, the French and the Danish. The German system, by far the oldest, has undergone considerable changes. At the time it was instituted, the bulk of insurance relief was compensation for loss of wages due to incapacitating sickness, now medical service is the primary benefit. The British system has existed nationally since 1911, the government took over the system under which private "Friendly Societies" had long been operating. France, also, before the adoption in 1930 of her national law on social insurance, had long experience with voluntary and private associations for sickness insurance. The French system is notable for the large part which physicians had in dictating its terms. There, the physician is paid by the patient, who is reimbursed (up to 85 per cent) by his insurance fund. The system in Denmark is nominally voluntary, but social and economic pressure makes it in effect compulsory.

All four of these systems include only people in the lowest economic brackets. The author feels it to be desirable to cover also classes higher in the economic scale.

The relative merits of voluntary and compulsory insurance are studied exhaustively. There is really no purely voluntary and modern system in existence. The author—in contradistinction to the majority of the Committee on the Costs of Medical Care, which felt that the State was not justified in compelling payment of funds until there could be an equivalent guarantee for adequate service—says “Instead of organizing for the payment of medical costs after having achieved improvement of service, society must organize for payment in order to achieve improvement of service.”

The last chapter, *Some Basic Principles for an American Program*, is an excellent and even masterly summation.

*Patologia Comparata della Tuberculosis*, April 28, 1935, vol 1, no 1, (A cura dell'Istituto Vaccinogeno Antitubercolare, Director Prof Alberto Ascoli) (Supplemento della Rivista Biochimica e Terapia Sperimentale)

By FLORENCE R. SABIN

We have been asked to review a new Italian journal on tuberculosis, in order to introduce it to the American medical public. The first number of this Journal of Comparative Pathology of Tuberculosis, edited by Professor Alberto Ascoli and published under the auspices of the Istituto Vaccinogeno Antitubercolare, appeared on the 28th of April, 1935. It is devoted almost exclusively to the subject of vaccination with the Bacillus Calmette-Guérin.

The first article, entitled *Esperimenti di raffronto vaccinale*, is an account of the preliminary experiment on the “vaccinal antitubercular comparison” performed by the Istituto Vaccinogeno Antitubercolare at Guinzano. It describes the vaccination of one calf at birth with 50 mgm of BCG subcutaneously, and of a second intravenously with 500 mgm of a virulent heat-killed bovine organism. These two calves were then inoculated with 5 mgm of the same virulent living culture, together with two controls. The calf which had received the BCG showed a high degree of resistance to the subsequent inoculation, the calf which had received the heat-killed organisms developed a spontaneous infection even before it was inoculated, and the controls developed tuberculosis.

The second article, by Dante Pansera, entitled *Azione protettiva del B C G contro la tubercolosi spontanea della cavia*, describes an experiment in which twenty guinea pigs vaccinated with BCG were kept in a pen with twenty pigs which had been inoculated with virulent bovine tubercle bacilli intraperitoneally, and fifteen which had been inoculated with the same strain subcutaneously, and twenty which had neither been vaccinated nor inoculated. The number of cases of spontaneous tuberculosis was followed. Of the normal

controls, eight died of intercurrent infections. The experiment was followed for 10 months, in 8 months, palpable inguinal lymph nodes were found in some of the nonvaccinated group, and by 10 months all of these controls, twelve in number, had tuberculous lesions, proved by transmitting the disease to other guinea pigs. During this time none of the group vaccinated with the BCG developed lesions, proved by the failure to infect other guinea pigs with their lymph nodes. These data are all given in tables.

These two articles cover 38 pages. There then follows a short paper by M. Carpano, entitled *Su di un nuovo metodo di colorazione del bacillo tubercolare*, which gives a procedure for staining tubercle bacilli, consisting in the use of carbol-fuchsin, decolorization with weak sulphuric acid, counterstaining with vesuvina, and subsequent treatment with iodine. This procedure allows a greater analysis of the structure of the bacillus than the usual technique.

More than half of the first *Fascicolo*, 121 pages, is taken up with an extensive bibliography concerning the work with BCG.

#### *Brief Comment*

F. J. BENTLEY *Artificial pneumothorax: experience of the London County Council Medical Research Council, Special Report Series no 215. Pp 94, London, His Majesty's Stationery Office, 1936, paper, 1s, 6d.*

It would be a most interesting task to write a lengthy abstract of this study. But a review of it can have only one aim, and that is to say, in the most emphatic manner, everybody at all interested in pneumothorax treatment must read this work. It contains, more than any other monograph on this subject, a wealth of information on practically all those points in pneumothorax treatment that are of practical interest and that can be expressed statistically. It is eminently a book written *sine ira et studio*. One must ponder over all its many tables, and out of the apparently dry statistical presentation will come a vivid realization of much that is important in indication, prognosis and results, more vivid, and certainly more convincing than mere impressionistic data (of which there is plenty in the literature) and more instructive than the lusty discussions between the adherents and the opponents of the method.

*Diseases of the respiratory tract. Clinical Lectures of the Eighth Annual Graduate Fortnight of the New York Academy of Medicine. By 21 contributors, with 56 illustrations, pp 418, Philadelphia and London, W. B. Saunders Co., 1936, cloth, \$5.50.*

This collection of papers covers in concise and authoritative essays practically all those morbid conditions of the respiratory tract that offer the most important differential diagnostic problems in tuberculosis work. In addition, there are three papers specifically concerned with tuberculosis. The table of contents is indicative of the field covered. E. H. Pool, Opening remarks, M. A.

Ramirez, The relation of allergy to the diseases of the respiratory tract, A R Dochez, Common cold, C T Porter, Sinus disease from infancy to old age, C J Imperatori, Diseases of the larynx, trachea and main bronchi, C L Jackson, Bronchoscopy in relation to diseases of the respiratory tract, J B Amberson, Jr, Bronchiectasis, H T Chickering, Influenza of the respiratory tract, J C Meakins, Chronic pneumonitis, C H Smith, Pneumonia in childhood, J A Miller, The evolution of pulmonary tuberculosis, A R Rich, Immunity in tuberculosis, A V S Lambert, Surgery of tuberculosis of the chest, L U Gardner, Pneumococcosis with particular reference to silicosis and tuberculosis, D Riesman, Emphysema, H Lihenthal, Chronic nontuberculous empyema notes for the physician and the general surgeon, H Wessler, Abscess and gangrene of the lungs, G Blumer, Pulmonary thrombosis and embolism, Y Henderson, Atelectasis, massive collapse, and related postoperative conditions, L F Craver, Carcinoma of the lung, H S Martland, Diseases of the mediastinum

A R SHANDS *Handbook of orthopaedic surgery* In collaboration with R B Raney With 169 illustrations, pp 503, C V Mosby Co, St Louis, 1937, cloth, \$5 00

This recent book on orthopaedic surgery has been written primarily for the medical student, the text has been divided into twenty-four parts to be readily adaptable to undergraduate curricula. The authors have freely utilized the work of many orthopaedic surgeons and have attempted to set up a guide for study. For its purpose the book should prove useful. The text is clear and has been written with simplicity and candor, the illustrations are excellent and reflect the simplicity of the text. The good selective bibliography will doubtless prove to be useful to the practitioner whose interest in orthopaedic problems requires him to know more about diagnosis and treatment than can be supplied in a book which is little more than a guide to instruction.

FRANK KELLNER *Die "atypische" Pneumonie, eine klinisch-chronologische und differential-diagnostische Studie, zugleich ein Beitrag zur Frage der "Grippe" und des Frühinfiltrats* With five plates, vol 6 of *Immunität, Allergie und Infektionskrankheiten*, pp 52, München, Verlag der Ärztlichen Rundschau, Otto Gmelin, 1936, paper, R M 2 70

A brief, but rather thorough discussion of more or less fleeting pulmonary infiltrations, with particular emphasis on their differential diagnostic significance in relation to tuberculous infiltrates.

JOSÉ SILVEIRA *Questões de Tuberculose* With a preface by Cardoso Fontes, 1 Serie, pp 242, with many illustrations, Argeu Costa & Cia, Bahia, Brazil, 1936, paper, Rs 30\$000



This is a loose collection of papers dealing with various practical problems in the clinic of tuberculosis. As Dr. Cardozo Fontes points out in his preface, the collaborators intend to discuss such matters from a modern point of view. José Silveira devotes three chapters to the discussion of aurotherapy with a number of different gold compounds. Eduardo de Araujo reports on BCG vaccination of 1700 newborn in the city of Bahia. Castro Lima presents the clinical and pathological findings in a case of haematogenous tuberculosis of the larynx. Silveira and Alves discuss the association of asthma and pulmonary tuberculosis. In the final chapter, Silveira and Marback report three patients in whom Horner's syndrome was observed, following alcoholization of the phrenic nerve. The book is well edited, many roentgenograms illustrate the text and a large bibliography is added. The authors succeed well in bringing into a clear relief the various problems arising from clinical observations of pulmonary tuberculosis. The subjects are discussed from a modern point of view and a good account of present-day opinion together with a generous discussion of the observation in a large tuberculosis department are assembled by the collaboration of the various authors.

HEINRICH GERHARTZ *Multiple Sklerose und Tuberkulose. Tuberkulose-Bibliothek, edited by Franz Redeker and Karl Diehl, No. 58, pp. 48, Johann Ambrosius Barth, Leipzig, 1935, paper, Mk. 4.80.*

This is an elaborate, and possibly a labored attempt to prove that multiple sclerosis is a "metatuberculous disease." The arguments are based largely on the literature and are collected in an ingenious, but sometimes rather far-fetched manner. A total of 175 literature references are marshalled in support of the author's thesis. This study is interesting, at times more in its sidelines than in regard to the main argument. The impression of the monograph as a whole is more impressive than convincing, but well worth reading.

HANNES SALMENKALLIO *Über Die Komplementbindungsreaktion von Witebsky, Klingenstein und Kuhn. Über Ihre Spezifität und Bedeutung, speziell bei Lungentuberkulose. Pp. 106, Acta Societatis Medicorum Fennicae "Duodecim," Ser. A, Tom. xiv Fasc. 2, Helsinki, 1936, paper.*

This test was performed on some 1600 blood samples from more than 1300 patients, about half of whom did not have clinical tuberculosis. While the total percentage of positive reactions was not unsatisfactory, only about 28 per cent of patients with minimal lesions yielded positive results. As far as a positive diagnosis is concerned, the old experience is repeated that only in patients with far-advanced lesions is the percentage of positive fixations high enough to be of any diagnostic aid. When, then, a negative reaction is no indication whatsoever to rule out clinical tuberculosis, a positive reaction does not prove clinical tuberculosis, since about 20 per cent of patients with poly-

arthritis, more than 10 per cent of syphilitics and 3 per cent of normals reacted positively. In the present thorough studies with a refined technique and antigen that is supposed to be in a particularly felicitous position between the unavoidable Charybdis of specificity and Scylla of sensitivity, the results remain essentially the same as those with earlier and less elaborate procedures of complement-fixation encouraging in that group of patients in whom a serological diagnosis is not needed, practically useless in that group in which additional diagnostic help would be welcome.

H. KURTEN, Direktor der Medizinischen Poliklinik der Universität München. *Zur Diagnostik, Therapie und Prognostik der Lungentuberkulose im Altertum und Mittelalter*. Pp. 20, *Praktische Tuberkulose-Bucherei, Beihefte Des Deutschen Tuberkulose-Blattes*. Herausgegeben von Prof. Dr. Kurt Klare, 14. Heft, Georg Thieme, Leipzig, 1936, paper, R. M. 1.30.

This is a very brief and rather loose-jointed collection of citations from Hippocratic teachings up to the late Middle Ages, concerning the subject matter mentioned in the title. The occasion for this essay seems to be the author's interest in the teachings about tuberculosis of a municipal physician of Memmingen, Ulrich Ellenbog, who wrote a consultant's advice in the year 1480. There is, unfortunately, no reference to the original source. Ellenbog seemed to have been a more shrewd than wise believer in eclecticism without—as far as presented in this study—any original thought.

FRANK HAMMOND KRUSEN. *Light Therapy With frontispiece and 42 illustrations in the text. Second Edition, revised and enlarged*. Pp. xx + 238, Paul B. Hoeber, Inc., New York, 1937, cloth, \$3.50.

The first edition of this book was critically and extensively reviewed in the January, 1934, issue of the *Review* (vol. 29, no. 1). The entire book has evidently been gone over carefully, much new material has been added, the bibliography more than doubled, and errors and omissions corrected. In particular the chapter on physiology, which in the previous edition was quite inadequate, has been considerably expanded. That a second edition appears indicates that many persons have found Doctor Krusen's work stimulating and helpful, a by no means inconsiderable tribute in the face of a confusing and difficult subject. This new and improved volume, in which Doctor Krusen's infectious and continued enthusiasm everywhere abounds, should prove of greater popularity.

*Surgeon Errant, the Life and Writings of William Henry Bucher, 1874-1934*. Edited by Emil Bogen. With 45 illustrations, pp. vii + 212, Los Angeles, California, The Angelus Press, 1935, cloth, \$2.00.

This book is a collection of autobiographical material of Doctor William Henry

Bucher whose eventful life was crowned by the fruitful work he did in Olive View Sanatorium, of which he was Superintendent from 1921 until his death in 1934. Doctor Emil Bogen has edited the book and prefaced it by a brief biographical sketch. The editorial work is of a high order of reference and excellence, and the entire make-up is beautiful and dignified. The wide professional travels of Doctor Bucher make interesting reading since he was a keen observer and an active physician. Here is much that is of real value to the student of the development in American medicine and of the tuberculosis movement.

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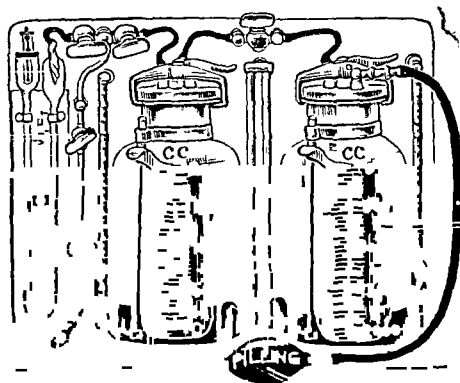


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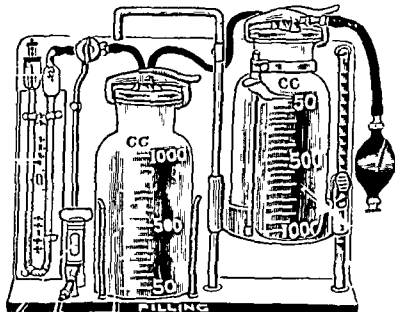
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### *The Table of Contents for the July issue will be selected from the following articles*

MCDUGALL, J B, AND CRAWFORD,  
J H Tomography

NONIDEZ, JOSÉ F, AND KAHN,  
MORTON C Experimental Tu-  
berculosis Infection in the Tad-  
pole and the Mechanism of Its  
Spread

RYAN, W J, AND MEDLLR, E M  
Coexistence of Lymphocytic  
Leukaemia and Far-Advanced  
Pulmonary Tuberculosis

STEINER, MORRIS, GREENE, MERI-  
DIAN R, AND KRAMER, BEN-  
JAMIN The Effect of Vitamin-A  
Deficiency on Experimental Tu-  
berculosis in the Guinea Pig and  
Rabbit

MASTEN, A R The Sedimentation  
Rate and Medlar's Index

LIANAN, ERNEST B, AND ERICKS,  
WALTER P Precipitation of  
Water Soluble Tuberculo-protein  
by Hydrogen-Ion Concentration

BANYAI, ANDREW L Topical Ap-  
plication of Codliver Oil in Tuber-  
culosis

KOROI, EPHRAIM Paracardiac Pul-  
monary Emphysema

TODD, LUCIUS N The Relation of  
Intrapleural Pressures to the For-  
mation of Effusions in Artificial  
Pneumothorax

JACOBS, M, AND BELOFT, H M  
Transthoracic Treatment of Tu-  
berculous Cavities

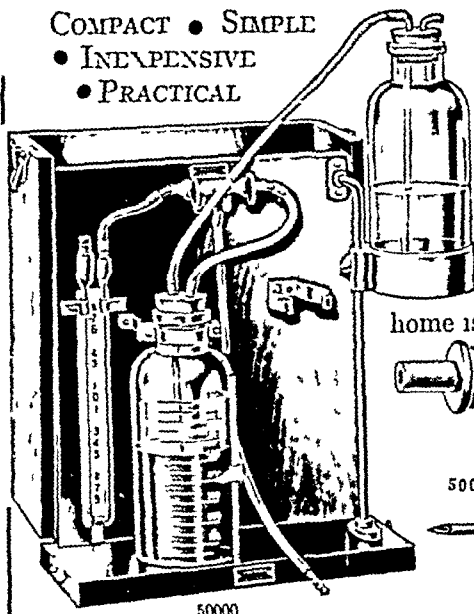
BERGHAUSEN, OSCAR Acacia Solution  
in the Treatment of Pulmonary  
Haemorrhage

FRANK, LORENZ W Tuberculous  
Peritonitis

BEATTY, OREN A Manifestations of  
Undulant Fever in the Respira-  
tory Tract

EDITORIAL  
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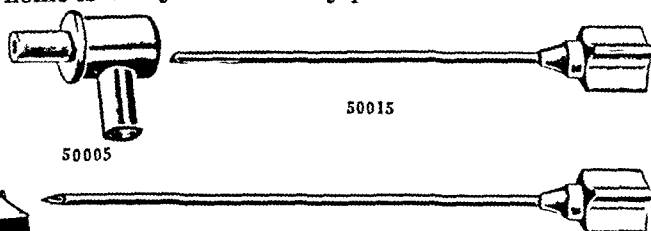


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# INDEX OF AUTHORS

## A

- AARON, THEODORE H , 59 701-706  
 ABEL, HANS, 65 128-141, 67 45-58, 69 26-36, 1057-1058, 70 901-902, 1042-1053, 72 143-150, 74 293-294, 75 41-52, 78 725-734, 79 359-363  
 ABELMAN, WALTER E , 67 755-778  
 ABERNATHY, ROBERT S , 70 547-556, 557-569  
 ABO, TAKASHI, 77 519-523  
 ABRAHAM, JEROME, 70 285-295  
 ABRAHAMOWITZ, SOL, 65 465-476, 68 127-135, 76 320-321, 80 902-903  
 ABRAMSON, SAMUEL, 59 1-9, 168-185, 186-197, 198-218, 61 765-797, 65 631-634, 783-785, 73 315-329  
 ABSHER, W K , 59 643-649  
 ACETO, JOSEPH N , 68 157-164, 799-802, 74 641-644  
 ACHARYA, B K , 78 203-225, 80 871-875  
 ACKERMAN, ALFRED J , 61 299-322, 63 176-193, 255-274, 399-416  
 ACKERMAN, HELEN, 60 359-365  
 ACREE, PAGE W , 70 61-70, 763-783  
 ADAIR, CHARLES V , 64 207-217  
 ADAIR, FOSTER, 66 378-380  
 ADAMS, RALPH, 59 353-363  
 ADCOCK, JOHN D , 61 705-718, 66 58-62, 69 543-553  
 ADDINGTON, MILTON C , 70 476-482  
 ADHIKARI, PRASANT K , 80 825-832  
 ADIAO, AMPARO C , 79 31-40  
 ADLER, DENIS C , 69 940-956  
 AFFLECK, MARGARET N , 75 519-520, 78 226-234  
 AFFRONTI, LEWIS F , 79 284-295  
 AGAR, HILDA D , 67 217-231  
 AGIUS, E , 72 53-63  
 AGOSTINI, EARL E , 77 356-358  
 AGRESS, HARRY, 69 824-828  
 AHN, A K , 78 815-821  
 AJELLO, LIBERO, 78 576-582  
 AKAWIE, SHIRLEY, 60 439-447, 448-454  
 ALBRECHT, F KENNETH, 60 532-535  
 ALDRIDGE, CLIFTON, 80 267-268  
 ALEXANDER, A F , 80 (Supplement, July 141-146)  
 ALEXANDER, HATTIE, 74 (Supplement, August 232-240)  
 ALEXANDER, JOHN, 61 57-59  
 ALEXANDER, ROBERT S , 65 505-510  
 ALLAMANIS, J , 73 964-965, 74 (Supplement, August 197-208)  
 ALLEN, ALBERT R , 79 680, 80 446-447  
 ALLEN, GEORGE S , 74 581-589  
 ALLEN, HARRY S , 68 136-143  
 ALLEN, ROYAL L , JR , 77 184-188  
 ALLEN, SINCLAIR T , JR , 77 848-857  
 ALLEY, FRANK H , 63 381-398  
 ALLGOWER, MARTIN, 59 562-566  
 ALI, JOSEPH H , 80 914  
 ALLING, DAVID W , 68 37-49, 70 15-31, 995-1008, 71 519-528  
 ALLISON, MARVIN J , 59 168-185, 186-197, 198-218  
 ALLISON, STANTON T , 62 563-571, 65 612-616, 72 552-554, 74 400-409, 79 102-104  
 ALLMARK, M G , 68 199-207  
 ALT, W J , 74 388-399  
 ALTMAN, DAVID P , 80 876-885  
 ALTMANN, VLADIMIR, 77 221-231  
 AIVERTSON, CLARA, 69 419-442  
 ALWAY, ROBERT, 71 765-766  
 AMANO, S , 71 465-472  
 AMATUZIO, DONALD S , 66 228-232, 357-363  
 AMBERSON, J BURNS, 61 518-524, 69 520-542  
 AMERICAN TRUDEAU SOCIETY, 59 106-112, 140, 60 681-682, 61 145-157, 274-299, 436-440, 760-764, 62 451-454, 556-561, 63 230, 496-500, 617-624, 729, 64 125-126, 223, 323-326, 476, 579-582, 65 100-110, 219-220, 351-356, 494-504, 643-653, 786-791, 66 104-123, 251-260, 389, 503-508, 641-649, 781-782, 67 114-122, 268-271, 396-399, 550-552, 679-705, 68 150-155, 302-306, 477-503, 636-655, 808-838, 946-973, 69 131-152, 313-317, 477-478, 649-655, 854-858, 1068-1073, 70 184-189, 380-381, 540-546, 756-761, 930-953, 1105-1110, 71 148-161, 326-332, 464, 607, 771-773, 904-926, 72 137-141, 256, 408-418, 559-567, 699-711, 73 145-156, 310-313, 449-450, 607-608, 790-794, 970-975, 74 163-168, 307-308, 484, 647-653, 814-819, 980-984, 75 157-168, 352-357, 524-528, 697-698, 859-864, 1012-1018, 76 164-166, 326-329, 513-515, 708-713, 920-929, 1112-1117, 77 191-201, 371-373, 553-560, 728, 874-875, 1036, 78 145-150, 285-331, 490-497, 655-660, 814, 957-960, 79 108-118, 258-263, 387-398, 549, 684-697, 822-852, 80 115-123, 282, 452-455, 597, 764, 921-924  
 AMES, WENDELL R , 68 9-23  
 AMIDON, E L , 77 848-857  
 AMILL, LUIS A , 60 514-519  
 AMRHEIN, ILA J , 66 436-448  
 ANASTASEA, K N , 70 139-148  
 ANASTASIADIS, ANASTASIOS A , 76 388-397, 588-600  
 ANDER, L , 76 983-987  
 ANDERSON, AUGUSTUS E , 71 503-518  
 ANDERSON, GAYLORD W , 67 123-131  
 ANDERSON, HARRY S , 68 382-392  
 ANDERSON, LEIGHTON L , 69 71-77, 72 653-658  
 ANDERSON, LUCIA E , 63 7-16  
 ANDERSON, ROBERT J , 70 593-600, 71 406-418  
 ANDERSON, RUDOLPH J , 71 609-616

- ANDRIGH, H S, 78-611-616  
 ANDRIWE, NEIL C, 71 871-881, 77 62-72, 78 839-847  
 ANDRIS, PAUL M, 62 170-175  
 ANGEL, R W, 71 889-891  
 ANGELO, FRANKLIN L, 61 717-750  
 ANGLINE, D MURRAY, 68 657-677  
 ANGHILLI, B, 79 522-524  
 ANGRIST, ALFRED A, 73 110-116  
 ANGUS, DARRELL C, 70 166-170  
 ANNO, HISATO, 71 333-348  
 ANTHONY, ELEANOR, 70 1030-1041  
 AOYAMA, K, 67 545-546  
 AQUINAS, MARY (SISTER), 76 215-224  
 ARANT, L S, 61 881-882, 71 807, 78 632  
 ARMADA, ORLANDO, 68 871-884  
 ARMSTRONG, A RUFFY, 70 907-909, 75 338-339  
 ARMSTRONG, B W, 71 219-239  
 ARMSTRONG, FRANK L, 68 238-248, 71 193-200, 72 242-244, 73 776-778, 77 113-117  
 ARONSON, M H, 69 26-36, 1057-1058, 70 1042-1053, 75 11-52, 461-468  
 ARONSON, CHARLOTTE FERGUSON, 68 713-726  
 ARONSON, DAVID L, 79 83-86  
 ARONSON, JOSEPH D, 62 408-417, 63 121-139, 717, 68 695-712, 713-726, 70 71-90, 72 35-52, 245, 74 7-14, 810-811, 79 83-86, 731-737  
 ASSELINEAU, J, 67 853-858  
 ATTINGER, ERNST O, 74 210-219, 220-228, 77 1-9, 80 38-45, 46-52, 53-58  
 ATWELL, ROBERT J, 75 846-848, 76 877-879, 880-887, 78 127-130, 399-402, 927-931  
 ATCHINCLOSS, J HOWLAND, JR, 76 22-32, 77 863-866, 78 191-202  
 AUERBACH, OSCAR, 59 601-618, 60 604-620, 61 845-861, 62 324-330, 64 419-429, 67 173-200, 70 191-218, 527-530, 71 165-185, 72 386-389, 75 242-258, 76 988-1001, 80 207-215  
 AYVAZIAN, JOHN H, 76 1-21  
 AYVAZIAN, L FRED, 60 305-331
- B**  
 BABCOCK, CLAUDE E, 70 109-120  
 BABIONE, ROBERT W, 62 518-524  
 BACHMAN, HENRY, 79 87-89  
 BACKERMAN, TOBEY, 69 173-191  
 BACOS, JAMES M, 67 201-211  
 BADGER, THEODORE L, 60 305-331, 65 1-23, 67 568-597, 755-778, 779-797, 74 317-342, 75 648-649  
 BAGBY, B B, 66 436-448  
 BAI, ANGEL F, 69 554-565  
 BAISDEN, LOUIS A, 68 425-438, 439-443, 444-450  
 BALA, JOHN, 68 42-47, 71 860-866  
 BALDRIDGE, G DOUGLAS, 63 672-673, 674-678  
 BALDWIN, EDWARD R, Bibliography, 62 (Supplement, July 114-119)
- BALDWIN, R W, 68 372-381  
 BAITER, ABRAHAM M, 67 232-246, 68 782-785  
 BAN, BINDRA, 72 71-90, 76 799-810  
 BANKIER, J D H, 68 400-410  
 BARACH, AVAN L, 66 778-780  
 BARBER, LOUIS M, 68 926-932, 73 882-891  
 BARRISPI, M, 72 315-355  
 BARROUR, BLANCH F, 77 172-176  
 BARCLAY, RALPH K, 69 957-962  
 BARCLAY, WILLIAM R, 60 385-386, 67 490-496, 68 794-795, 70 784-792, 71 556-565, 72 236-241, 713-717, 78 760-768, 79 543-544  
 BARRIST, ELIUS M, 61 735-737  
 BARRY, VINCENT C, 71 783-798, 73 219-228, 74 798-801, 75 476-487, 77 952-967, 78 62-73  
 BARSHAY, B, 66 605-614  
 BARTMAN, K, 74 475-476, 77 999-1004, 79 97-101  
 BARTON, HARRY C, 71 30-48  
 BARTZ, QUENTIN R, 63 4-6  
 BASS, H E, 59 632-635, 60 520-523, 61 158, 62 219-222  
 BASTARRACHEA, FERNANDO, 77 473-481, 79 246-250  
 BATES, DAVID V, 80 (Supplement, July 172-178)  
 BATES, RICHARD C, 63 332-338  
 BATTAGLIA, BIAGIO, 66 594-600  
 BATTEN, JOHN, 72 851-855  
 BAUM, GEORGE L, 74 624-632  
 BAUM, GERALD L, 77 162-167  
 BAUM, LEWIS F, 59 68-75  
 BAUM, OTTO S, 59 68-75  
 BAUMGARTNER, LEONA, 79 687-689  
 BAYAN, A, 66 219-227  
 BEACHAM, EDMUND G, 66 213-218, 68 136-143  
 BEALL, GILDON N, 80 716-723  
 BEARDSLEY, FREDERICK A, 59 402-414  
 BEASLEY, CARROLL, 69 599-603  
 BEATTY, ARCH J, 62 434-438  
 BECK, CLAUDE S, 71 904-924  
 BECK, FREDERICK, 62 58-66, 66 44-51, 68 238-248, 72 151-157, 242-244, 79 134-141, 80 738-743  
 BECKER, BARNEY B, 67 22-28, 69 636-637  
 BECKER, HAROLD J, 70 806-811  
 BECKER, M L, 76 892-895  
 BECKLAKE, MARGARET R, 76 398-409, 77 209-220, 400-412, 79 457-467  
 BEESON, PAUL B, 62 403-407  
 BEHNISCH, ROBERT, 61 1-7  
 BEKKER, J H, 74 633-637  
 BELL, J CARROLL, 69 71-77, 75 992-994, 995-998, 76 152-158, 683-691, 80 108-110  
 BELL, JOHN W, 73 123-127, 74 169-177, 75 538-552, 77 593-604, 78 848-861  
 BELLOWES, MARJORIE, 66 666-679  
 BENNETT, RICHARD H, 62 128-143  
 BENNETT, WARREN A, 76 503-505  
 BENSON, ELLIS S, 59 415-428

- BENSON, LOUIS, 69 595-598  
 BENSON, R. E., 72 201-209, 76 225-231  
 BENSON, W. M., 65 376-391  
 BENTLEY FRANCIS J., 70 759-763  
 BERNARD, LeROI, 69 570-588  
 BERTER, BERNARD A., 59 656-663  
 BIRKSFORD, O. D., 77 323-328  
 BERG, GEORGE S., 74 121-127  
 BERGLI, LESLIE R., 69 406-418  
 BIRGH, N. P., 75 710-723, 76 983-987  
 BERGMANN, MARTIN, 72 268-273  
 BERGMQUIST, SAUL, 61 112-117  
 BERGR, MALCOLM E., 75 581-587  
 BERKE, RICHARD A., 59 632-635, 61 411  
 BERNIN, LOUIS, 70 577-592  
 BERNATZ, PHILIP E., 74 954-957  
 BERNSTEIN, I. LEONARD, 77 162-167  
 BERNSTEIN, JACK, 69 539, 63 556-567, 65 357-364, 67 351-365 366-375  
 BERNSTEIN, SIDNEY, 62 101-108, 63 119-125, 66 36-43, 70 370-372, 73 266-275  
 BERNSTEIN, THEODORF C., 62 654-666  
 BERRY, J. W., 69 51-61  
 BERRY, JAMES L., 71 961-967  
 BERRY, JOHN W., 72 373-380  
 BERTF, STEPHEN J., 74 171, 78 773-778, 779-784, 79 344-350  
 BERTHAUX, SOLANGE, 72 330-339  
 BERTHONG, MORGAN, 77 436-449, 79 221-231  
 BEUTNER, E. H., 78 637-643  
 BEYER, ALFRED M., 72 381-385  
 BHARGAVA, R. K., 76 110-125  
 BHATTACHARIA, B. K., 69 62-77  
 BIEHL, J. PARK, 68 296-297, 70 266-273, 430-441, 77 605-622  
 BIGGS, RAY H., 66 364-372  
 BINCKLEY, FREDERICK M., 69 788-793  
 BIONDO, THOMAS, 76 761-769  
 BIRATH, G., 66 134-150, 75 699-709, 710-723, 721-729, 76 983-987  
 BIRD, KENNETH T., 75 529-537, 77 669-674, 675-680  
 BIRKELAND, JORGEN M., 61 556-559, 64 332, 520-533, 74 229-238, 239-244  
 BIRKHAUG, KONRAD, 59 567-588, 60 547-556, 63 85-95, 613-614, 66 335-344, 68 96-102, 188-198, 69 300-303, 511-519, 70 873-880  
 BIRNBAUM, STANLEY J., 78 697-711  
 BIRSNER, J. W., 70 109-120  
 BJORNESJO, K. B., 73 967  
 BLACK, J. M., 73 805-817  
 BLACK, J. P. MILES, 69 396-405  
 BLACK, JOYCE, 65 272-277, 67 657-664  
 BLACK, THOMAS C., 61 335-345, 826-834, 68 615-621  
 BLADES, BRIAN B., 60 683-698  
 BLAIR, EMIL, 74 343-350, 78 1-7  
 BLAKER, ROBERT G., 79 152-179, 180-203  
 BLALOCK, F. A., 77 764-777  
 BLANKENBERG, HERMAN W., 79 357-361  
 BLATT, NORMAN H., 69 192-201  
 BLAZSIK, C. F., 79 773-779  
 BLINCOFF, W., 71 898-899  
 BLITZ, OSCAR, 62 213-218  
 BLOCH, HUBERT, 59 562-566, 61 270-271, 67 629-643, 828-852, 853-855, 68 731-738, 71 112-125, 228-218, 75 488-491, 495-500, 80 911  
 BLOCH, ROBERT G., 59 551-561, 77 245-259  
 BLOCK, JEROML, 68 382-392  
 BLOMQUIST, EDWARD T., 77 172-176  
 BLOOMER, WILLIAM E., 61 316-352  
 BLOUNT, S. GILBERT, JR., 69 71-77, 80 (Supplement, July 128-130)  
 BLOUMENTHAL, B. J., 79 761-772  
 BOAK, RUTH A., 68 31-41, 70 344-348  
 BOBROWITZ, I. D., 66 750-757  
 BOCKING, DOUGLAS, 69 1002-1015  
 BOGARDUS, GEORGE M., 71 280-290  
 BOGFA, EMIL, 59 707-709, 61 226-216, 62 160-169, 63 190-192, 64 192-196, 67 676-677, 68 31-41, 69 396-405, 70 311-318, 71 153-155, 76 435-450, 912-914, 1110-1111  
 BOGGER, WILLIAM P., 61 862-867, 62 610-617, 64 153-160  
 BOJALIL, L. F., 77 173-181, 543-545, 79 246-250, 80 554-558  
 BOLLINGER, BETTY, 62 300-306  
 BOLTES, BEN, 61 738-741  
 BOND, JAMES O., 80 188-199  
 BONDI, AMFEDO, JR., 63 325-331, 65 272-277, 67 657-664  
 BONDURANT, STUART, 70 547-556, 570-576  
 BOONF, IRVINE U., 76 568-578  
 BORDEN, CRAIG W., 68 177-187  
 BORN, H. G., 71 178-187, 79 764-772  
 BORIF, JEANNE M., 77 511-515  
 BORNSTFIN, SIEGBERT, 61 353-354, 68 796-798  
 BOSMAN, A. RAE, 76 398-409  
 BOSSO, LOUIS, 78 788-792  
 BOSWELL, HENRY, 66 364-372  
 BOSWORTH, EDWARD B., 69 37-49, 930-939, 70 15-31, 995-1008, 71 519-528  
 BOUCOT, KATHARINE R., 62 501-511, 65 (Supplement, January 1-50), 69 164-172  
 BOUGAS, JAMES A., 75 865-884  
 BOVORNKITTI, SOMCHAI, 74 (Supplement, August 246-255), 77 39-61, 271-289  
 BOWEN, JOHN F., 80 426-430  
 BOWER, GEORGE C., 78 468-473, 80 (Supplement, July 207-208)  
 BOWERMAN, E. P., 75 259-265  
 BOWMAN, B. U., JR., 73 907-916, 80 232-239  
 BOYACK, GERALD A., 75 584-587  
 BOYAR-MANSTEIN, MARIAL L., 63 694-705  
 BOYD, LINN J., 75 553-575  
 BOYNTON, RUTH E., 73 620-636, 75 442-460  
 BOZALIS, GEORGE S., 59 289-310  
 BRADLEY, ELIZABETH M., 62 101-108

- BRAHAM, STANLEY, 61 518-521  
 BRANTIGAN, OTTO C, 59 210-238, 80 (Supplement, July 191-201)  
 BRASHFELT, CHARLES A, 73 609-619, 75 938-948  
 BRATTON, A C, JR, 63 7-16  
 BRAY, HARRY A, 69 634-635  
 BRICKNER, I ALFRED, 78 8-16  
 BREFFS, ATLANTA G, 67 106-107  
 BREITE, MELVIN J, 79 672  
 BREITENBUCHER, ROBERT B, 66 228-232, 357-363  
 BRETEL, J, 68 467-470, 75 650-655  
 BRIEFER, J, 69 26-36, 70 363-366, 1012-1053, 75 11-52, 78 725-734  
 BREWER, LYMAN A, III, 60 119-138, 69 554-565  
 BREWER, WILLIAM D, 60 455-465  
 BRIDGE, ETRA V, 64 682-685, 74 581-589, 78 647-649, 749-752  
 BRINKMAN, GREGORY L, 69 458-463, 963-967, 80 732-737  
 BRISCOE, W A, 80 (Supplement, July 136-137)  
 BRISSAUD, H E, 71 (Supplement, August 221-224), 80 326-339  
 BRISTOL, LEONARD J, 68 65-71  
 BRITT, CLARENCE I, 78 839-847  
 BROFMAN, BERNARD L, 71 904-924  
 BRONSON, S MARTIN, 76 173-191  
 BROOKE WILLIAMS, R D, 67 732-754  
 BROSBEE, EDWIN A, 73 123-127, 266-275  
 BROTHERS, GEORGE E, 59 364-390  
 BROUET, G, 79 6-18  
 BROWN, CHARLES D, 76 426-434, 78 794-798  
 BROWN, HALLA, 74 783-792  
 BROWN, HENRY A, 63 427-433  
 BROWN, HORACE D, 70 806-811, 74 59-67, 78-83  
 BROWN, JOHN W, 62 543-548  
 BROWN, LEE B, 73 79-98  
 BROWN, W, 80 (Supplement, July 155-157)  
 BROWN, WALTER B, 68 286-289, 73 593-596  
 BROWNE, NOEL C, 77 952-967  
 BROWNING, ROBERT H, 75 846-848, 76 777-779, 880-887  
 BRUCE, ROBERT A, 59 364-390, 62 29-44  
 BRUECKNER, HAROLD H, 69 759-762  
 BRUHIN, H, 80 559-568  
 BRUKARDT, DIANE T, 77 387-399  
 BRUM, VICTOR C, 76 33-46  
 BRUMFIEL, DANIEL M, 62 (Supplement, July 98-103)  
 BRISON, VERNON, 62 286-299, 65 768-770, 68 280-283, 631-633, 69 267-279  
 BUCHBERG, ABRAHAM S, 59 624-631, 77 245-259  
 BUCHTEL, BUELL C, 76 291-297  
 BUCK, MARGARET, 65 759-760  
 BUCKINGHAM, WILLIAM W, 62 434-438  
 BUCKLES, MAURICE G, 64 394-407  
 BUDD, VERA, 64 81-86, 68 557-563, 71 860-866, 72 539-542, 76 272-278  
 BUECHNER, HOWARD A, 68 775-781, 71 503-518  
 BURCHER, EDWIN V, 79 622-630, 631-640  
 BURNETT, LOUIS, 68 902-911  
 BUDGIN, WALTER I, 62 712-517  
 BUGB, ELIZABETH I, 60 366-376  
 BUIHNER, VICTOR B, 71 71-87, 73 917-929  
 BLUM, K G, 69 455-457  
 BUMGARDNER, JOHN R, 71 137-139, 72 659-662  
 BLUMF, ROSE, 61 20-38  
 BLUM, PAUL A, 61 263-268, 64 197-206, 207-217, 66 175-187, 67 652-656, 69 1016-1021, 1051-1053, 74 128-141, 76 703-705, 79 72-77  
 BURDON, KENNETH L, 64 170-181  
 BURGER, FREDERICK J, 65 519-522, 635-636  
 BURKE, HUGH D, 62 48-67, 79 52-65  
 BURKE, JOHN C, 65 392-401, 67 644-651  
 BURKI, RICHARD M, 75 921-937  
 BURNETT, JAMES M, 64 71-76  
 BURNETT, C A, 71 856-873  
 BURRILL, ROBERT G, 74 229-238, 239-244, 78 259-267  
 BURROWS, BENJAMIN, 78 760-768, 79 543-544  
 BUSFMAN, UTE, 73 547-562  
 BUSH, D, 62 638-644  
 BUSHBY, S R M, 72 123-125  
 BUTLER, KATHARINE, 74 136-141
- ## C
- CABELLI, VICTOR J, 69 604-611, 76 697-702  
 CACCESE, ANTHONY, 66 52-57  
 CACCIA, P A, 75 105-110, 76 1071-1078  
 CADDEN, A V, 62 645-653  
 CADE, ROBERT, 71 693-703  
 CALDEN, GEORGE, 67 722-731, 68 523-534, 70 483-489, 72 633-646, 73 338-350, 74 964-967, 77 311-322  
 CALDWELL, DAVID M, 77 644-661  
 CALIN, ARTHUR A, 68 382-392, 69 334-350, 70 304-311  
 CALLANAN, J G, 74 358-366  
 CALWELL, H G, 73 301-305  
 CAMERON, GEORGE F, 64 564-571  
 CAMERON, HAMILTON, 70 533-537  
 CAMERON, VIRGINIA, 60 393-405  
 CAMMEN, MERRILL N, 60 439-447, 448-454  
 CAMPAGNA, MAURICE, 69 334-350  
 CAMPBELL, GUY D, 66 364-372  
 CANADA, ROBERT O, 62 518-524, 563-571  
 CANETTI, GEORGES, 74 (Supplement, August 13-21), 75 650-655, 79 684-686  
 CAPLE, L H, 68 622-624  
 CARABASI, ROBERT J, 78 610-622, 79 543  
 CARABASSO, B, 71 867-876  
 CARABELLI, A ALBERT, 77 22-31  
 CARMICHAEL, ELIZABETH, 68 199-207  
 CARNEIRO, JOSÉ FERNANDO, 79 544-545  
 CARPENTER, CHARLES M, 60 359-365, 68 31-41, 70 344-348, 74 152, 79 374-377

- CARR, DAVID T , 63 427-433, 65 159-167, 69 78-83,  
70 899-900, 74 954-957, 76 503-505, 78 647-  
649,749-752,753-759
- CARRETERO, ROSARIO, 74 (Supplement, Au-  
gust 246-255), 77 39-61
- CARROLL, D G , 71 249-259
- CARROLL, DOUGLAS, 63 231-251, 64 583-601
- CARROLL, J D , 71 302-304
- CARSTENSEN, BO, 61 613-620, 67 258-260
- CARTER, MAX G , 69 1042-1044
- CARTON, ROBERT W , 76 167-172
- CARVAJAL, ENEDINA J , 76 1094-1096
- CARVAJAL, GUILLERMO, 76 1094-1096
- CASTILLO, HERMILO DEL, 73 61-71
- CATTANEO, C , 75 793-806
- CAWTHON, WILLIAM U , 65 429-442, 66 391-415,  
68 791-793
- CEDERQUIST, DENA C , 60 455-465
- CELIS, ALEJANDRO, 71 810-821
- CERBÓN, S J , 80 554-558
- CERIOTTI, GIOVANNI, 69 104-110
- CHADWICK, R M , 72 356-366
- CHAIKOF, LEO, 80 732-737
- CHAMBERLAIN, W EDWARD, 69 566-584
- CHAMBERS, JOHN S , 76 852-861
- CHAMBERS, JOHN S , JR , 63 625-643
- CHANDRASEKHAR, S , 77 1030-1032
- CHANG, Y T , 63 100-107, 68 119-126, 79 673-  
676,805-809
- CHAPMAN, GEORGE, 74 783-792
- CHAPMAN, JESSE P , 71 137-139
- CHAPMAN, JOHN S , 71 459-461, 73 422-433
- CHAPMAN, PAUL T , 66 151-160
- CHAREN, SOL, 73 438-441
- CHARNEY, JESSE, 64 577-578
- CHARR, ROBERT, 67 376-384, 71 877-884
- CHARTER, WILBUR V , 62 563-571
- CHAVES, AARON D , 59 469-480, 63 194-201,  
65 128-141, 67 45-58,598-603, 69 26-36, 70 363-  
366,901-902,1042-1053, 72 143-150, 74 293-296,  
75 41-52, 76 732-751, 77 359-363,516-518,725-  
734, 80 585-586
- CHEN, GRAHAM, 59 692-700
- CHEVALIER, J , 79 6-18
- CHIEN, JAMES T T , 69 818-823
- CHILDRESS, WILLIAM G , 62 144-148, 63 339-345,  
65 692-708, 66 621-622
- CH'IU, PHILIP T Y , 60 483-486
- CHOPRA, I C , 70 328-333
- CHOREMIS, C B , 70 139-148, 72 527-536,859-  
862, 73 964-965, 74 (Supplement, August 197-  
208), 76 263-271, 79 522-524
- CHOUCROUN, NINE, 59 710-712
- CHOY, SUN HAK, 73 99-109
- CHRISTIAN, EDWARD R , 67 247-257, 70 1083-1091
- CHRISTIE, FREDERICK J , 63 312-324
- CICERO, RAUL, 71 810-821, 73 61-71
- CINCOTTI, J J , 75 730-744
- CITRON, K M , 80 167-180
- CLAGETT, THERON O , 61 193-200, 65 159-167,  
74 581-589
- CLAPS, FRANCIS X , 76 862-866
- CLARK, CHARLES M , 66 391-415
- CLARK, MARY E , 68 786-787, 80 744-746
- CLARKE, BARBARA L , 69 92-103, 991-1001
- CLARKE, EDMUND R , JR , 69 351-369, 73 795-804
- CLARKE, ROBERT W , 71 596-599, 72 694
- CLAUDON, DANN B , 71 144-145
- CLAUSS, ROY H , 74 351-357
- CLAYTON, Y M , 80 167-180
- CLEMONS, HELFN, 62 618-631, 67 732-754
- CLERF, L H , 61 60-65
- CLINE, F , JR , 59 643-649
- COATES, E OSBORNE, 65 754-758, 69 458-463
- COBURN, FRANK E , 71 299-301
- COCCHI, CESARE, 74 (Supplement, August 209-216)
- COHEN, AARON A , 79 253-255
- COHEN, ARCHIBALD C , 62 539-542
- COHEN, DAVID H , 61 582-585
- COHEN, GOODMAN, 71 249-259
- COHEN, JACK D , 65 1-23
- COHEN, ROBERT V , 71 220-227
- COHEN, S S , 59 113-127
- COHEN, SAMUEL, 59 519-538, 62 360-373, 68 165-  
176
- COHEN, SUMNER S , 68 229-237, 70 739-742,  
78 106-110,899-905
- COHN, J E , 71 249-259
- COHN, JEROME, 78 682-691
- COHN, M L , 60 269-271, 63 108-115, 70 465-  
475,641-664,852-872,1030-1041, 72 693, 75 656-  
658
- COLE, CLARENCE R , 63 538-546
- COLE, FRANCIS H , 71 295-298, 75 259-269
- COLE, LEON R , 80 398-403
- COLE, MILTON B , 80 915-918
- COLE, ROGER M , 62 403-407
- COLEMAN, C M , 74 42-49
- COLEMAN, CHARLES M , 69 1062
- COLLIN, E , 79 484-491
- COLLINS, D M , 70 274-284
- COLLINS, MARTHA D , 61 257-262
- COLM, ANN C , 63 372-380
- COLMORE, HENRY P , 69 618-624
- COLWELL, CHARLOTTE A , 63 679-693, 71 272-279,  
73 892-906, 75 678-683
- COMER, J V , 66 605-614, 70 191-218
- COMSTOCK, GEORGE W , 73 157-164, 77 877-907,  
79 542
- CONALTY, MICHAEL L , 71 785-798,799-809,73 219-  
228, 75 476-487, 77 952-967, 78 62-73
- CONANT, JAMES S , 71 349-360
- CONANT, N F , 61 690-704, 70 498-503
- CONE, ROSS B , 67 509-513
- CONGE, G , 79 484-491
- CONKLIN, WILLIAM S , 68 885-901



- CONNORS, CONSTANCE J , 68 470-471, 69 128  
 CONWAY, JOHN D , 66 601-601  
 CONZEIMAN, GAILORD M , Jr , 74 739-716, 802-806  
 COOK, LEIGH, JR , 65 741-753  
 COOKE, GEORGE M , 71 371-381  
 COOLEY, DENTON A , 68 727-733  
 COOLEY, JAMES AILEN , 59 650-655  
 COOPER, DAVID A , 65 (Supplement, January 1-50), 75 122-131  
 COOPER, PHILIP, 74 729-738  
 COPE, J H , 61 443-464  
 COPE, JEROME A , 74 92-98  
 CORAI, STEVEN, 80 264-266  
 CORCORAN, THOMAS E , 80 911  
 CORPE, RAYMOND F , 73 681-689, 74 92-98, 75 199-222, 223-241, 77 73-82, 764-777, 80 388-397  
 CORPER, H J , 60 269-271, 63 103-115, 65 722-734  
 COSTER, J F , 74 958-960  
 COSTIGAN, WILLIAM J , 68 65-74  
 COTTON, BERT H , 70 109-120  
 COUNIHAN, HENRY E , 73 219-228  
 COURNAUD, ANDRE, 63 231-251, 64 583-601  
 COWAN, DONALD, 73 620-636, 75 442-460  
 CRAGE, WILLIAM D , 59 78-85  
 CRANDALL, ARCHIE, 74 457-461  
 CRANDALL, WILLIAM D , 59 325-335  
 CREGER, WILLIAM P , 60 343-353  
 CREITZ, JOSEPH, 71 126-130  
 CRELLIN, J ANTRIM, 69 657-672  
 CRENSHAW, GERALD L , 71 30-48  
 CRIEP, LEO H , 59 701-706, 67 535-537  
 CRISALLI, JOSEPH P , 79 531-532  
 CROCE, PIETRO, 73 785-786  
 CROFTON, JOHN, 77 869-871  
 CROMBIE, D W , 62 170-175  
 CROSS, D F , 72 228-230  
 CROW, HORACE E , 75 199-222  
 CROW, JOHN B , 67 859-868  
 CROWLE, ALFRED J , 77 290-300, 681-693, 80 (Supplement, July 153-154)  
 CRUMB, CRETYL, 65 201-205  
 CUGELL, DAVID W , 67 568-597, 74 317-342  
 CUIZON, ROD, 77 858-862  
 CULLEN, JAMES H , 72 231-235, 74 289-292, 76 33-46  
 CUMMEROW, ELIZABETH H , 66 335-344  
 CUMMINGS, MARTIN, 59 599, 60 228-235, 621-627, 628-633, 62 484-490, 632-637, 63 459-469, 65 596-602, 603-611, 66 345-350, 378-380, 70 637-640, 72 117-118, 685-686, 856-858, 73 246-250  
 CUMMINS, CHRISTOPHER, 74 188-195  
 CURRERI, ANTHONY R , 59 10-29, 74 29-41  
 CURRY, FRANCIS J , 73 501-518, 77 749-763  
 CURRY, JOSEPH L , 69 657-672  
 CURTIS, GEORGE M , 66 699-721  
 CURTIS, JOHN K , 72 569-576, 75 745-755  
 CUSHING, IVAN E , 79 315-322  
 CUSTFR, EDWARD W , 79 378-381  
 CUTHBERT, JAMES, 61 662-677  
 CUTLER, J W , 71 600-603  
 CUYKENDALL, JAMES H , 72 373-380  
 CYSEFR, ERNA, 65 779-782  
 CZAJA, Z GEORGE, 75 295-302
- ## D
- DAIL, M C , 69 464-468  
 DAILEY, JAMES E , 78 478-484  
 DALY, JOHN F , 76 588-600  
 DAMROSCH, DOUGLAS S , 74 (Supplement, August 232)  
 DANELATOU, C , 72 859-862  
 DANGLE, GERTRUDE, 70 349-359, 72 143-150, 74 293-296  
 DANIELS, GEORGE E , 62 532-538  
 DANIELS, J , 71 88-96, 97-111  
 DANIELS, MARC, 61 751-756  
 DARRICARRERE, RAFAEL, 68 96-102  
 DARZINS, E , 80 866-870  
 DASCOMB, HARRY E , 77 511-515  
 DASHER, WILLIAM A , 69 396-405  
 DAYEY, WINTHROP N , 61 705-718, 63 332-338, 66 58-62, 69 543-553, 70 623-636  
 DAVIDOFF, EUGENE, 62 532-538  
 DAVIDSON, HORACE B , 64 394-407  
 DAVIDSON, J , 74 485-510  
 DAVIES, PAMELA A , 77 271-289  
 DAVILS, ROBERTS, 75 768-780, 80 188-199  
 DAVIN, JULIA R , 61 643-647  
 DAVIS, BERNARD B , 65 631-634  
 DAVIS, EDGAR W , 74 106-111  
 DAVIS, J DWIGHT, 60 288-304, 62 525-531  
 DAVIS, MARTIN W , 52 594-609  
 DAVIS, REYNOLDS, 77 350-355  
 DAVIS, W E , JR , 72 345-355  
 DAY, GEORGE H , 68 634-635, 69 847-851, 73 597  
 DAYTON, ROY, 62 (Supplement, July 104-113)  
 DEAKINS, DUANE D , 68 926-932, 73 882-891  
 DE ALENQUER, MARIO, 78 462-467  
 DEBAKEY, MICHAEL E , 68 727-733  
 DEBRE, ROBERT, 65 168-180, 72 869-870, 74 (Supplement, August 191-196, 221-224), 80 326-339  
 DECAMP, PAUL T , 70 61-70, 77 496-500  
 DECKER, ALFRED M , JR , 75 538-552  
 DECKER, JOHN P , 75 122-134  
 DEEB, EDWARD N , 72 543-547  
 DE FIGUEIREDO, FLAVIO POPPE, 76 871-876  
 DEIBERT, KIRK R , 75 139-144  
 DEICHES, HELEN, 68 631-633  
 DEISS, WILLIAM P , 62 543-548  
 DE J MACIAS, JOSÉ, 79 265-272  
 DE LA HUERGA, J , 77 120-133  
 DEL CASTILLO, HERMILO, 73 61-71  
 DEMETRIADES, ANDREAS D , 75 326-330  
 DEMONTE, A J H , 70 328-333

- DEMPSEY, MARY, 66 109-116, 68 177-187, 70 296-303  
 DENARO, SALVATORE A , 74 462-463  
 DENICOLA, RALPH, 62 128-143  
 DENNENY, JOAN M , 71 785-798, 75 476-487  
 DENNERLINE, RICHARD L , 76 752-760  
 DENST, JOHN, 64 489-498, 68 144-149, 70 1030-1041, 71 441-446, 73 944-955  
 DE PAOLA, DOMINGOS, 71 186-192, 76 871-876, 78 140-144  
 DE PINZON, TERESINA P , 67 522-525  
 DERBES, VINCENT J , 74 464-467, 79 251-252, 531-532  
 DES AUTELS, EUGENE J , 68 912-925  
 DESBORDES, JEAN, 66 382-383  
 D'ESOPPO, NICHOLAS D , 62 563-571  
 DES PREZ, ROGER, 75 659-666, 77 539-542, 80 431-433  
 DESSAU, FREDERICK I , 60 223-227, 65 519-522, 523-546, 635-636  
 DEUSCHLE, KURT, 69 319-333, 70 228-265, 743-747, 71 316-317, 72 851-855, 75 659-666, 76 1100-1105, 1106-1109, 77 539-542, 80 200-206, 415-423, 431-443, 904-908  
 DE VESTY, GERALDINE, 77 1005-1011  
 DEVINE, KENNETH D , 73 52-60  
 DEWING, STEPHEN B , 60 25-31  
 DEWITT, C W , 64 322  
 DEWLETT, HAL J , 78 773-778, 779-784, 79 344-350  
 DEYKE, VERN F , 63 275-294  
 DHOPESHWARKAR, G A , 78 117-120  
 DIAZ, RAPHAEL M , 77 221-231  
 DICARA, LEO V 71 755-761  
 DICKIE, HELEN A , 59 10-29, 70 102-108, 72 690-692, 74 29-41  
 DIDCOCK, K A , 74 1-6  
 DIEFENBACH, WILLIAM C L , 62 390-402  
 DIENA, B B , 78 785-787, 79 816-817  
 DI FONZO, MARIA, 66 240-243  
 DILLON, ANN, 65 111-127, 70 1009-1019  
 DILLON, EDWARD S , 65 (Supplement, January 1-50)  
 DILLON, ROBERT F , 71 529-543  
 DILLON, ROBERT J , 73 165-190  
 DIXON, KENDAL C , 77 106-119  
 DIXSON, SHIRLEY, 79 492-496  
 DOANE, EDWIN A , 64 192-196  
 DOCKSEY, JOHN W , 71 573-583  
 DOERNER, ALEXANDER A , 64 564-571  
 DOLL, JAMES P , 80 262-263  
 DOLLEY, FRANK S , 60 419-438  
 DOMAGE, GERHARD, 61 8-19  
 DOMM, SHELDON E , 74 188-195  
 DOMON, CHARLES M , 60 564-575, 68 103-118  
 DONIKIAN, MARY A , 67 808-827, 69 173-191, 72 846-850  
 DONNERBERG, ROY L , 75 846-848, 76 877-879, 880-887  
 DONOHUE, ROBERT F , 80 590-593  
 DONOSO, H , 71 249-259  
 DONOVICK, RICHARD, 60 90-108, 109-120, 121-130, 140-142, 539, 63 556-567, 65 761-764, 66 219-227, 67 354-365, 366-375, 68 284-285  
 DOONEIEF, A S , 59 624-631, 60 557-563, 70 178, 219-227, 72 252  
 DOPPELT, HARRY B , 60 189-205  
 DOTTER, CHARLES T , 62 353-359  
 DOUB, LEONARD, 61 407-421, 77 301-310  
 DOUGLAS, R GORDON, 70 49-60, 78 697-711  
 DOUGLASS, BRUCE E , 63 427-433, 74 954-957  
 DOUGLASS, RICHMOND, 60 524-526, 69 930-939  
 DOUTHIT, VERA B , 79 543  
 DOWLING, HARRY F , 69 192-204  
 DOY, C H , 79 492-496  
 DOYLE, W , 78 637-643  
 DOZIER, SLATER M , 75 949-953, 954-957  
 DRAKE, CLIFFORD L , 79 374-377  
 DRASH, E CATO, 73 79-98  
 DREA, W F , 74 145-146  
 DREISHPOON, IRVING H , 70 49-60  
 DRESSLER, SIDNEY H , 64 489-498, 70 504-508, 1030-1041, 1102-1103, 71 390-405, 441-446, 73 944-955, 74 (Supplement, August 188-190), 80 111-112  
 DROBECK, BERYL, 64 197-206, 207-217, 66 175-187  
 DROLET, GODIAS, J , 61 39-50, 72 419-452  
 DROSOS, CH , 76 263-271  
 DRUMMOND, ELEANOR E , 76 579-587  
 DRUMMOND, MARGARET, 59 599  
 DRUSCH, HELENE E , 68 31-41  
 DUBIN, ALVIN, 77 120-133  
 DUBOCZKY, BELA O , 70 1092-1095  
 DUBOS, RENE J , 60 384, 385, 670-674, 63 119, 65 637-640, 67 874-877, 68 1-8, 70 391-401, 73 781-784, 74 117-120, (Supplement, August 1-6), 541-551, 655-666, 667-682, 683-698, 699-717, 79 80-82, 484-491  
 DUBOSE, HOWARD M , 66 345-350, 76 47-63  
 DUERR, EDITH L , 75 506-509  
 DUFFY, ROBERT W , 73 831-852  
 DUFOR, EMMA H , 62 77-86, 69 585-594, 71 704-721  
 DUKE, C JAMES, 80 590-593  
 DUMBOVICH, BORIS, 77 1017-1018  
 DUNBAR, FRANK P , 77 350-355, 79 669-671, 80 188-199  
 DUNHAM, WOLCOTT B , 72 119-122  
 DUNN, KATHARINE REMINGTON, 60 439-447, 448-454  
 DUNN, MAX S , 60 439-447, 448-454, 75 688-691  
 DUNNER, EDWARD, 62 563-571  
 DU PREEZ, L , 77 400-412  
 DUROST, H B , 71 201-219  
 DURR, FREDERICK E , 80 876-885  
 DURRANCE, JOHN R , 78 604-609  
 DUSHANE, JAMES W , 74 940-953

DUTTON, ROBERT, 78 191-202  
 DWORK, RALPH E, 60 15-50, 79 127-139  
 DWORSKI, MORRIS, 62 153-171, 69 766-789, 811-812  
 DYF, WILLIAM E, 61 719-721, 63 275-291, 295-311, 66 531-511, 67 106-107

## E

EARLY, LAWRENCE J A, 71 289-292  
 EASTMAN, GILFORD, 78 191-202  
 EATON, J LLOYD, 74 176-178  
 EBERT, RICHARD V, 68 177-187, 80 (Supplement, July 45-49, 169-171, 209-212)  
 EBERT, ROBERT H, 59 554-561, 65 64-74, 67 490-496, 68 791-795, 70 784-792, 71 556-565, 75 71-72  
 EDDIE, B, 71 566-571  
 EDGAR, JANICE, 76 331-345  
 EDGE, J R, 71 747-755  
 EDLING, J H, 74 128-135  
 EDWARD, DEIRDRE WALDRON, 77 952-967, 78 131-134  
 EDWARDS, HERBERT R, 61 39-50, 65 221-234, 66 666-679  
 EDWARDS, LIDIA B, 80 747-749  
 EDWARDS, PHYLLIS Q, 76 517-539, 77 546-550, 79 83-86  
 EFFLER, DONALD B, 63 252-254, 71 668-675, 775-784, 73 19-30, 75 469-475  
 EGAN, J B, 78 251-258  
 EHRENSHAFT, J L, 72 801-809  
 EHRLICH, JOHN, 63 4-6, 7-16  
 EICH, ROBERT H, 76 22-32, 77 863-866, 78 191-202  
 EICHENHOLZ, ALFRED, 71 473-502  
 EIDUS, L, 78 785-787, 79 816-817  
 EIDUSON, SAMUEL, 60 439-447, 448-454  
 EISENMAN, WILLIAM, 61 738-741  
 EISMAN, E A, 70 121-129, 130-138, 77 694-702, 703-711  
 ELIAS, FREDERICK, 66 750-757  
 ELKINS, CHARLES W, 63 227-229  
 ELLICOTT, MARJORIE F, 74 317-342  
 ELLIOTT, WILLIAM E, 69 604-611  
 ELLIS, CATHERINE, 74 (Supplement, August 232-240)  
 ELLIS, F HENRY, JR, 65 159-167, 74 581-589, 940-953  
 ELLISON, LOIS T, 80 181-187  
 ELLISON, OSCAR, 70 701-713  
 ELLISON, ROBERT G, 80 181-187  
 ELMENDORF, DUMONT F, JR, 65 429-442, 66 391-415, 70 228-265, 71 316-317  
 ELMORE, FRANCIS H, 61 95-105, 106-115  
 EL NAGAH, A M, 79 119-133  
 ELOESSER, L, 73 444-445  
 ELSBERG, SANFORD S, 65 655-672, 74 84-91  
 EMERSON, GEORGE L, 65 210-214  
 EMMART, E W, 59 438-448, 63 100-107, 68 220-228

ENG, R TAK, 72 356-366  
 ENGRAEK, HANS CHR, 75 347-348  
 ENGI I, D, 68 910-941  
 ENGI LIHARD, WARREN E, 76 279-285  
 ENTFRLINE, PHILIP D, 66 548-566, 70 593-600  
 EPSTEIN, ISRAEL G, 75 553-575, 78 815-821  
 EPSTEIN, JOSEPH G, 68 796-798  
 EPSTFIN, LAZAR, 66 90-91  
 ERIFMEYER, H, 67 629-643  
 ERLER, STANLEIGH, 69 1037-1041  
 ERICH, HENRY, 61 563-568  
 ERSKINE, FREDERICK A, 59 128-139  
 ERVIN, JOHN R, 71 775-784  
 ESCOVITZ, WILLIAM D, 66 373-377  
 ESLAMI, VALI, 78 127-130  
 EVANDER, L C, 78 637-643  
 EVANS, ELWIN, 61 335-345  
 EVANS, J R, 69 464-468  
 EVANS, JOHN A, 60 487-500  
 EVANS, ROBERT L, 70 296-303

## F

FABRICANT, CATHERINE G, 66 567-577  
 FABRICANT, JULIUS, 66 567-577  
 FABRIZIO, ANGELINA M, 65 250-271, 66 314-334  
 FAHLBERG, WILLSON J, 76 896  
 FALE, ABRAHAM, 64 159-169, 66 228-232, 357-363, 509-521, 68 177-187, 70 689-700, 74 367-375, 897-902  
 FALOON, WILLIAM W, 68 207-211  
 FALOR, WILLIAM H, 70 166-170  
 FARBER, JASON E, 62 109-111, 63 67-75  
 FARID, Z, 79 119-133  
 FAUCHER, I O, 73 576-580, 75 670-674  
 FAYEZ, G, 80 26-37  
 FAYOUR, CUTTING B, 60 212-222, 72 577-600, 73 581-585  
 FEINBERG, RICHARD J, 67 103-105  
 FEIND, CARL R, 60 39-44  
 FELD, DAVID D, 59 317-324  
 FELDMAN, JOSE, 74 158-159  
 FELDMAN, WILLIAM H, 62 149-155, 345-352, 66 477-485, 722-731, 67 341-353, 68 75-81, 575-582, 69 859-868, 71 752-754, 75 266-279  
 FELDMANN, FLOYD M, 61 892, 63 721, 71 140-143  
 FELLOWS, HINES HAROLD, 60 487-500  
 FELTON, FRANCES G, 80 267-268  
 FENGER, E P K, 59 113-127, 78 106-110  
 FENNER, FRANK, 63 714-716, 64 353-350, 68 321-341, 342-371, 73 650-673, 76 76-89  
 FERARU, FELIX, 79 577-590  
 FEREBEE, SHIRLEY H, 66 632-635, 67 108-113, 539-543, 68 264-269, 70 521-526, 73 1-18, 74 917-939, 80 371-387  
 FERGUS, EMILY B, 79 659-662  
 FERNÁNDEZ, MARTHA, 73 61-71  
 FERRER, M IRENÉ, 80 510-521

- FETTER, B F , 70 498-503  
 FETTERHOFF, K I , 66 501  
 FIDLER, W F , 64 307-312  
 FILLEY, GILFS F , 80 (Supplement, July 213)  
 FINESTONE, ALBERT J , 64 630-644  
 FINKBINER, RODMAN B , 75 122-134  
 FINLAI, A C , 63 1-3  
 FIORE, JOHN M , 74 289-292  
 FIRESTONE, GEORGE M , 59 415-428  
 FISCHER, D ARVIN, 78 604-609  
 FISCHER, HERBERT K , 76 880-887  
 FISH, CHARLES H , 65 187-193  
 FISHER, BRUCE M , 64 557-563  
 FISHER, DON L , 73 134-138  
 FISHER, HYMAN, 61 257-262  
 FISHER, MYRON W , 66 626-628, 758-761, 69 469-470, 797-805  
 FISHLER, J STUART, 62 144-148  
 FITE, G L , 68 220-228  
 FITZPATRICK, FLORENCE K , 68 451-454, 77 867-868  
 FITZPATRICK, MARTIN J , 69 370-382, 72 675-684, 77 387-399  
 FITZPATRICK, WILLIAM J , 60 660-669  
 FIELDE, AUDREY L , 75 347-348  
 FLEISCHNER, FELIX G , 62 45-57  
 FLETCHER, C M , 80 483-494  
 FLOREY, M ETHEL, 65 547-571, 73 818-830  
 FLYNN, PAUL F , 69 50-57  
 FOGARTY, JOHN E , 78 661-666  
 FOLEY, JOHN A , 74 277-283  
 FOLTZ, ELDON L , 74 835-855  
 FORD, RALPH V , 68 541-547  
 FORD, WILLIAM B , 73 134-138  
 FORDHAM, GEORGE F , 62 428-433  
 FORNEY, JOHN E , 69 241-246  
 FORREST, ELIZABETH S , 68 786-787, 80 744-746  
 FORSE, MAX A , 78 268-273  
 FOURNIER, ETIENNE, 66 382-383  
 FOWLER, EDMUND P , JR , 60 39-44  
 FOWLER, WARD S , 72 783-800, 80 (Supplement, July 118-120)  
 FOX, JOHN A , 75 584-587  
 FOX, R T , 78 822-831  
 FOX, THEODORE H , 60 249-257  
 FOX, WALLACE, 71 314-315, 317-318  
 FRANCIS, JOHN, 73 276-290, 748-763  
 FRANK, BERNARD, 73 966  
 FRANK, N ROBERT, 67 568-597, 755-778, 71 676-692, 80 806-824  
 FRAPPIER, ARMAND, 79 296-306  
 FRASER, RICHARD S , 75 999-1002  
 FRAWLEY, THOMAS F , 70 841-851  
 FREED, C C , 76 398-409  
 FREDMAN, BENJAMIN, 60 258-263  
 FREIMAN, DAVID G , 59 449-460  
 FREMMING, BENJAMIN D , 72 204-209, 76 225-231  
 FREMONT, R E , 63 591-596  
 FREMONT SMITH, PAUL, 60 212-222  
 FREUND, JULIUS, 79 87-89  
 FREY, W H , 60 269-271  
 FRIEDLANDER, RALPH, 60 189-205  
 FRIEDMAN, ALAN J , 77 338-345  
 FRIEDMAN, BERNARD L , 79 265-272  
 FRIEDMAN, ELI, 60 354-358, 61 442  
 FRIEDMAN, EMANUEL, 72 833-839  
 FRIEDMAN, LORRAINE, 74 147-148, 245-248  
 FRIEDMAN, MAX M , 63 213-219, 64 448-452  
 FRIEDMAN, NATHAN, 76 123-131  
 FRIEDRICH, T , 79 351-356  
 FRISCH, ARTHUR W , 64 551-556, 65 278-288, 289-301, 302-315  
 FRITTS, HARRI W , JR , 80 (Supplement, July 131)  
 FROBISHER, MARTIN, JR , 60 621-627, 67 497-502, 530-534, 68 419-424  
 FROEB, HERMAN F , 77 737-748  
 FROELICH, ERNEST J , 78 74-82  
 FROMAN, SEYMOUR, 76 435-450, 964-969, 77 1030-1032  
 FROSTAD, SIMON, 79 597-605  
 FRUHLINGER, BEN, 68 42-47  
 FRY, DONALD L , 80 (Supplement, July 123-125)  
 FRY, LOIS, 73 547-562  
 FRY, WESLEY, 71 30-48  
 FUJIKAWA, Y FRED, 66 246-250  
 FUJITA, YUTAKA, 78 884-898  
 FUNK, V K , 59 113-127  
 FURCOLOW, MICHAEL L , 64 468-469, 68 307-320, 69 234-240, 73 609-619, 75 938-948, 78 667-681  
 FUSIA, DONALD A , JR , 65 744-753  
 FUSILLO, M , 69 464-468  
 FUSILLO, MATTHEW H , 75 949-953, 954-957, 76 507-508, 78 793
- G**
- GABY, WILLIAM L , 65 272-277, 67 657-664  
 GAENSLER, EDWARD A , 62 17-28, 63 547-555, 64 256-278, 67 3-21, 568-597, 755-778, 779-797, 74 317-342, 75 730-744, 80 (Supplement, July 185-193)  
 GAFFNEY, ETHNA E , 71 785-798, 799-809  
 GAGE, ROBERT P , 69 78-83, 70 899-900, 73 52-60  
 GAGLIARDO, FRANK J , 64 675-681, 66 762-764  
 GAHWYLER, MAX, 72 659-662  
 GAINER, JOSEPH H , 62 149-155, 345-352, 63 36-43  
 GALBRAITH, ELIZABETH H , 71 596-599  
 GALE, DAVID, 73 139-141, 77 1005-1011, 1012-1016, 80 95-99  
 GALE, GODFREY L , 66 732-743, 70 610-622, 75 410-419  
 GALE, JOSEPH W , 59 10-29, 62 543-548, 74 977  
 GALIHER, CLAUDIA B , 59 494-510  
 GALLAHER, B SHANNON, 80 181-187  
 GANCEDO, HECTOR A , 71 668-675  
 GANS, ROBERT H , 62 360-373

- GARATTINI, S, 80 110-111  
GARBIŃSKI, TADEUSZ, 77 1026-1029  
GARCIA RAMOS, J, 71 822-829, 73 519-528  
GARFINKEL, LAWRENCE, 76 988-1001  
GARGULAS, A, 76 263-271  
GARLAND, L H, 64 225-218  
GARMENT, EDWARD M, 68 796-798  
GARROD, LAWRENCE P, 62 582-585  
GARTHWAITE, BETTINA, 69 520-542  
GASS, R S, 65 111-127, 70 360-362, 1009-1019, 75 111-121  
GASTAMIDE-ODIER, M M, 75 843-845, 77 662-668, 79 94  
GEBAUER, PAUL W, 62 176-189, 80 6-11  
GEEVER, ERVING F, 61 422-425, 66 680-698  
GEIB, PHILIP O, 72 257-267  
GEMMILL, C L, 79 339-343  
GENSINI, GOFFREDO, 80 1-5  
GENTRY, W HAROLD, 66 95-98, 71 319  
GERBEAUX, J, 80 326-339  
GERE, J BREWSTER, 76 988-1001  
GERONIMUS, LIPPMAN H, 65 520-533  
GERSON, CHARLES E, 64 686-690  
GERSTL, B, 72 345-355, 79 212-220  
GETZ, HORACE R, 60 439-447, 448-454, 64 381-393, 72 218-227, 73 603-604  
GILBERT, ROBERT, 76 22-32, 77 863-866, 78 191  
GILBOY, JAMES T, 66 233-239  
GILMAN, RICHARD A, 70 734-738, 74 874-884  
GINSBURG, BEN, 75 688-691  
GISI, T A, 77 694-702, 703-711  
GITTENS, S AUBREY, 69 673-681, 79 307-314  
GLASER, STANLEY, 79 427-439  
GLASS, MACELLIS, 73 110-116  
GLASS, R, 69 1057-1058  
GLICK, MARY CATHERINE, 68 625-628  
GLICKLICH, MARVIN, 71 573-583  
GODDARD, JEAN, 69 595-598  
GOLBERG, MAURICIO, 74 (Supplement, August 267-278)  
GOLDBERG, JACOB, 60 189-205  
GOLDBERG, S I, 69 1057-1058  
GOLDMAN, ALFRED, 70 285-295, 76 123-131  
GOLDMAN, DEXTER S, 73 674-680  
GOLDMAN, ELISE CAHN, 73 674-680  
GOLDMAN, H I, 76 398-409, 79 457-467  
GOLDMAN, HOWARD L, 77 923-930  
GOLDMAN, HYMIE, 77 209-220  
GOLDMAN, MILTON, 70 149-154, 72 863-865, 76 909-911  
GOLDNER, MARTIN G, 65 589-595  
GOLDSMITH, JOHN R, 78 180-190  
GOLDSTEIN, GERALD, 74 783-792  
GOLDSTEIN, MERRILL M, 74 210-219, 220-228, 77 1-9  
GOLLEY, PAUL M, 60 377-382  
GOLOMB, JOSEPH, 62 441-445  
GOMEZ, FERNANDO D, 66 1-15  
GOMORI, GEORGE, 59 554-561, 61 560-562  
GONZALEZ-MENDOZA, AMADO, 77 543-545, 79 246-250  
GORDON, ARMOND, 64 50-63  
GORDON, BURGESS, 59 270-288, 61 201-225, 65 24-47  
GORDON, EDWARD D, 71 722-731  
GORDON, JOSEPH, 67 29-44  
GORDON, LEE, 72 64-70  
GORELICK, DAVID F, 63 346-354  
GOTSHALL, R Y, 62 475-480  
GOULD, DAVID M, 77 375-386  
GOULD, WILBUR J, 59 679-686  
GÜZSY, BÉLA, 73 442-443, 75 684-687  
GRADY, EDGAR D, 63 526-537  
GRANT, I W B, 74 485-510  
GRANVILLE, GEORGE E, 68 727-733  
GRASSET, EDMOND, 64 695  
GRAUB, MILTON, 61 735-737  
GRAY, DAVID F, 65 572-588, 68 82-95, 69 92-103, 991-1001, 72 171-195, 75 519-520, 78 226-234, 235-250  
GRAY, J A C, 75 833-835  
GRAY, J E, 77 976-982  
GRAYSTON, J THOMAS, 68 307-320  
GRAYZEL, DAVID M, 60 801-807  
GREEN, JOSEPH M, 72 633-646  
GREEN, ROBERT A, 79 790-798, 80 65-70, 833-844, 895-901  
GREENBERG, L, 78 785-787, 79 816-817  
GREENBERGER, MONROE E, 61 508-517  
GREER, J W, 79 119-133  
GREGG, ALAN, 67 517-521  
GREGOIRE, F, 71 867-876  
GREGORY, FRANCIS J, 60 366-376, 65 718-721  
GREGORY, LLOYD J, 69 58-64  
GRIBKOFF, GEORGE P, 70 916-919  
GRIFFIN, VIRGINIA L, 77 356-358  
GRIFFITH, LEWIS J, 74 462-463  
GRIFFITH, ROBERT L, 70 1020-1029  
GRIGG, E R N, 78 151-172, 426-453, 583-603  
GROSS, JOHN H, 77 506-510  
GROVES, LAURENCE K, 73 19-30  
GROW, J B, 70 1030-1041, 71 390-405  
GRUMBACH, FRANÇOISE, 79 1-5  
GRUNBERG, E, 67 674-675, 68 277-279, 71 898-899  
GRZYBOWSKI, STEFAN, 72 398-402, 73 305, 75 432-441  
GUILLAUME, ROBERT L, 69 745-758  
GULD, JOHANNES, 72 126-128, 74 297-303, 80 255-256  
GUNN, F D, 61 77-94  
GUPTA, K C, 70 328-333, 73 294-295, 296-300  
GUTEKUNT, R A, 62 116-117  
GUTHIEL, DOUGLAS, 62 645-653  
GUTHRIE, GEORGE, 67 432-439  
GUTIÉRREZ-VÁZQUEZ, J M, 74 50-58  
GYARFAS, WILLIAM, 70 285-295

## H

- HAAPANEN, JAAKKO H, 80 1-5  
 HAAS, ALBERT, 71 722-731  
 HADFIELD, WILLIAM J, 61 323-331  
 HACKNEY, ROBERT L, 63 103-118  
 HAENIG, ARTHUR W, 76 110-143  
 HAINSON, JAMES S, 69 113-130  
 HAKSTIAN, A, 70 535-536  
 HALFI, L D, 70 912-915, 71 219-257  
 HALEY, RAPHAEL R, 66 58-62, 69 513-553  
 HALL, H C, 75 807-822, 76 888-891, 77 815-822  
 HALL, WENDELL H, 71 178-180, 773-782, 79 518-521  
 HALLE, SHRA, 62 213-218  
 HALLETT, WILBUR Y, 80 716-723  
 HALLEY, T V, 63 41-48  
 HALPERN, B, 70 665-671  
 HALPERT, BENJ, 64 170-181, 68 727-733, 71 762-764  
 HAMBLETON, ARTHUR, 75 1007-1008, 76 159-160  
 HAMILTON, MARY ANNE, 66 680-698, 77 436-449, 79 221-231  
 HAMILTON, W F, 60 501-513, 80 181-187  
 HAMILTON, WILLIAM F, JR, 80 181-187  
 HAMMARSTEN, JAMES F, 78 391-398, 79 606-611  
 HAMMEL, JOSEPH V, 80 915-918  
 HAMRE, D, 66 219-227  
 HAN, LUNG SOO, 68 583-593  
 HAND, ETHEL M, 60 773-787  
 HANDY, VINCENT H, 59 78-85  
 HANKE, LILLIAN, 66 378-380  
 HANKE, JOHN H, 69 173-191, 74 597-607, 608-615, 77 789-801  
 HANLON, C ROLLINS, 65 48-63  
 HANSON, MARK, 64 159-169  
 HARDEN, K ALBERT, 63 103-118, 70 701-713  
 HARDY, ALBERT V, 80 188-199  
 HARDY, HARRIET L, 68 911-912, 72 129-132, 74 885-896  
 HARDY, KENNETH L, 73 451-471  
 HARENESS, J T, 61 443-464, 64 225-248, 249-255  
 HARRELL, DICK, 67 671-673  
 HARRELL, W K, 69 505-510  
 HARRIS, ALBERT H, 76 426-434  
 HARRIS, H WILLIAM, 71 126-130, 78 682-691, 944-948, 79 663-665  
 HARRIS, LEONARD C, 74 (Supplement, August 246-255)  
 HARRIS, MARVIN S, 76 123-131, 77 338-345  
 HARRIS, MILFORD D, JR, 76 225-231  
 HARRIS, T N, 59 186-197  
 HARRISON, HARLOW W, 69 554-565  
 HARROWER, J ROBERTS, 68 286-289, 73 593-596, 76 892-895  
 HART, P D'ARCY, 59 223-239  
 HARVEY, H P B, 77 492-495  
 HARVEY, REJANE M, 80 510-521  
 HARVEY, SIDNEY D, 74 533-540  
 HASENCLEVER, H F, 72 687-689  
 HASSFRT, G LEE, JR, 65 392-401  
 HATCH, H B, JR, 76 291-297  
 HATCH, HAROLD S, 67 232-246, 68 782-785  
 HAUG, WALTER A, 78 268-273  
 HAUSER, GEORGE, 69 334-350  
 HAUSMANN, PAUL F, 63 210-212  
 HAYERLAND, HARRY W, 74 112-116  
 HAWKINS, NORMAN G, 75 768-780  
 HAWLEY, WILLIAM L, 75 145-147, 76 906-908  
 HAYASHI, MITSUO, 79 371-373  
 HAYES, J N, 62 (Supplement, July 90-97)  
 HAYES, J W, 69 845-846  
 HAYRABETIAN, BERDJ, 68 165-176  
 HAZENHURST, GEORGE N, 71 1-11, 12-29  
 HEDAD, JEROME R, 60 1-14  
 HECKEL, JOHN, 69 307-308  
 HECKEL, ROBERT J, 61 798-808, 62 99-100, 63 718-720, 64 602-619  
 HEDBERG, GUSTAF A, 61 193-200  
 HEDGECOCK, LOYD W, 73 576-580, 75 670-674, 77 93-105  
 HEIKEN, CHARLES A, 63 480-486  
 HEKI, SHINICHIRO, 77 529-535  
 HELLER, ALFRED, 75 71-82  
 HELLER, M L, 75 730-744  
 HELLER, PAUL, 61 868-874  
 HEMANS, MARGARET J, 66 351-356  
 HEMINGWAY, ALLAN, 76 195-214  
 HEMPHILL, ROGER A, 66 261-270  
 HENDERSON, ALFRED R, 60 811  
 HENDERSON, HOWARD J, 64 381-393, 71 609-616  
 HENDERSON, RUTH W, 80 398-403  
 HENSLEY, NESTOR M, 76 132-139, 78 8-16  
 HENTEL, WILLIAM, 61 369-386, 63 476-479  
 HEPLAR, JOSEPH Q, 67 669-670  
 HEPPLESTON, A G, 59 198-218, 61 765-797  
 HERBEN, G F, 66 605-614  
 HERBUT, PETER A, 61 60-65  
 HERR, ROSS R, 75 584-587  
 HERRERA, VIVENCIO A, 74 277-283  
 HERRING, JACK L, 79 251-252, 531-532  
 HERSCHFUS, J A, 69 915-929  
 HERTZBERG, GERHARD, 62 118-119  
 HERTZMAN, VICTOR O, 65 443-450  
 HESS, ADELINE R, 62 481-483, 64 516-519, 73 892-906, 75 678-683  
 HEUCK, JULIA, 66 548-566  
 HEWELL, BARBARA, 69 733-744, 70 1064-1082  
 HEWITT, WILLARD C, 69 1054-1056  
 HICKAM, JOHN B, 74 309-316, 343-350, 78 1-7  
 HIGH, ROBERT H, 74 (Supplement, August 256-266)  
 HIGHTOWER, JOHN A, 69 58-64  
 HILL, GILBERT A, 75 849-850  
 HILL, HARRY E, 62 1-7, 76 132-139, 78 8-16  
 HILL, IDA, 63 487-489  
 HILLIS, B R, 74 485-510

- HILTZ, D M , 61 355-368  
 HILTZ, J E , 79 468-473  
 HIMMELSTEIN, AARON , 63 231-251, 64 583-601, 67 154-172  
 HINSHAW, H CORWIN , 59 140-167, 60 32-38, 61 145-157, 443-464, 64 225-248, 557-563, 68 263, 70 9-14, 71 752-754, 74 142-144  
 HINSON, K F W , 68 739-745  
 HIRSCH, A , 75 793-806  
 HIRSCH, JAMES G , 70 312-319, 955-976, 977-988, 989-994, 71 447-451, 732-742, 894-897, 75 331-337, 359-409  
 HITE, K EILEEN , 70 178, 219-227  
 HOBBY, GLADYS L , 59 219-220, 60 808-810, 63 1-3, 17-24, 434-440, 65 754-774, 67 808-827, 68 292-294, 69 173-191, 70 191-218, 527-530, 71 457-458, 72 367-372, 386-389, 846-850, 76 1031-1048, 78 934-938, 939-943, 80 274-276, 415-423  
 HOBSON, LAWRENCE B , 62 128-143  
 HOCHBERG, LEW A , 63 150-175  
 HOCHSTEIN, F , 63 1-3  
 HOCOTT, JOE B , 80 (Supplement, July 45-48)  
 HODGE, HAROLD C , 76 1063-1070  
 HOFFMAN, JOSEPH , 63 202-209  
 HOFFMAN, STANLEY H , 59 539-553  
 HOFFMANN, RICHARD , 67 798-807, 75 169-179  
 HOFMANN, GERALD N , 64 682-685  
 HOLDEN, H M , 60 654-659  
 HOLDING, BRUCE F , JR , 71 291-294  
 HOLIN, SABINE M , 79 427-439  
 HOLLAND, ROBERT H , 73 123-127  
 HOLLANDER, A GERSON , 67 497-502, 72 345-355, 438-551, 79 212-220  
 HOLLIFIELD, W C , 80 587-589  
 HOLLOWAY, JAMES B , JR , 60 228-235  
 HOLM, JOHANNES , 79 690-694  
 HOLMES, C X , 66 501  
 HOLMES, THOMAS H , 69 351-369, 73 795-804, 75 768-780  
 HOLMGREN, NELDA B , 59 102-105, 66 416-435  
 HOLZBERGER, PHILIP , 69 205-215  
 HONSKA, WALTER L , JR , 79 606  
 HOOD, R MAURICE , 78 21-37  
 HOPKINS, FREDERICK D , 65 494-503  
 HOPWOOD, LOUISE , 74 917-939  
 HORAVA, ALEXANDER , 67 677-678  
 HORNE, N W , 68 400-410  
 HOROWITZ, ISAAC , 63 346-354  
 HORSFALL, FRANK L , JR , 80 315-325  
 HORMAN, R K , 63 476-479  
 HORTON, GLENN E , 69 443-450, 73 704-715, 78 135-137, 80 724-731  
 HORTON, RALPH , 62 572-581, 66 16-27, 68 238-248, 71 193-200, 72 242-244, 77 413-417  
 HORWITZ, OLE , 80 659-675  
 HOSTY, THOMAS S , 78 576-582  
 HOUGLUM, BURTON , 69 406-418  
 HOUSTON, CHARLES , 80 (Supplement, July 213)  
 HOWARD, O P , 69 307-308  
 HOWARD, W LEONARD , 60 794-800, 63 140-149, 67 292-298, 70 518-520, 533-534, 71 766  
 HOWELL, JULIAN , 78 576-582  
 HOWLETT, KIRBY S , JR , 59 402-414, 63 312-324, 65 235-249, 68 270-272  
 HOYT, ANSON , 70 916-919, 75 618-623, 624-629, 76 752-760, 80 216-222  
 HSIE, JEN-YAH , 62 286-299  
 HSIUNG, G D , 70 912-915, 74 249-257  
 HUDGINS, PAUL C , 65 596-602, 603-611, 72 117-118, 340-344, 685-686, 856-858, 73 246-250, 75 83-92, 630-637, 78 138-139, 79 323-328, 382-383  
 HUDSON, HOLLAND , 66 104-108, 67 698-703  
 HUERGA, J DE LA , 77 120-133  
 HUGGIN, PERRI M , 79 204-211  
 HUGHES, FREDERIC J , JR , 63 295-311  
 HUGHES, HETTIE B , 67 798-807, 70 266-273  
 HUGHES, P G , 73 930-939  
 HUMPHREY, HAROLD I , 76 144-151  
 HUNTER, DON , 62 525-531  
 HUPPERT, MILTON , 76 451-467, 468-479, 77 1030-1031  
 HUPPLER, EDWARD G , 73 52-60  
 HURST, ALLAN , 64 489-498, 80 (Supplement, July 179-180)  
 HURWITZ, CHARLES , 62 87-90, 91-98, 638-644, 63 568-578, 68 127-135  
 HUSSEINI, HAIDAR , 65 655-672  
 HUTCHESON, R H , 65 111-127, 75 111-121  
 HUTCHINSON, JOANNE , 76 899-901  
 HUTCHISON, DORRIS , 60 78-89  
 HUIWARA, TOMEZO , 73 563-570  
 HWA, EUGENE C , 73 681-689  
 HYATT, ROBERT E , 80 (Supplement, July 138)  
 HYDE, BERNARD , 59 619-623, 61 883-886, 63 417-426  
 HYDE, LEROY , 59 619-623, 61 883-886, 62 525-531, 63 417-426, 69 1045-1050, 71 131-136, 78 906-915  
 HYMAN, GEORGE A , 59 539-553  
 HYMAN, MAURICE , 77 338-345
- I**  
 IBRAHIM, ABDULLA , 61 569-577  
 ILAND, C N , 68 372-381  
 ILASI, FRANK P , 66 436-448  
 ILAISKY, JAN , 65 777-778, 69 280-286  
 INADA, KIYOSHI , 79 232-237  
 IRONSON, ELLIOTT , 70 806-811, 74 59-67, 72-77  
 IRVINE, K NEVILLE , 74 (Supplement, August 43-49)  
 ISAWA, YUKIO , 74 253-276  
 ISHAK, K G , 79 119-133  
 ISRAEL, HAROLD L , 62 408-417, 64 453-460, 67 671-673, 69 846-847  
 ITO, KAORU , 72 393-397, 76 90-102, 77 529-535

ITO, RIO, 67 526-529  
 IVANOVICS, GEORGE, 77 1017-1018

## J

JABLON, SFYMOUR, 73 620-636, 75 442-460, 76 517-539  
 JACK, ALLYANDER, 77 1003-1011, 1012-1016  
 JACKSON, L L, 60 62-77  
 JACKSON, EDITH R, 69 119-142  
 JACKSON, JOAN K, 79 659-662  
 JACOBS, LEWIS G, 71 437-440  
 JACOBS, SYDNEY, 59 76-77, 68 382-392, 70 304-311, 71 464-467, 79 105, 251-252, 531-532  
 JACOBSON, GEORGE, 69 940-956, 71 590-596  
 JACOBSON, H R, 63 587-590  
 JACOB, RALPH F, 60 541-546  
 JAFFÉ, FREDERICK A, 61 182-191  
 JAFFE, HENRY L, 60 249-257  
 JAHN, RICHARD P, 65 88-92, 66 241-245, 80 78-84  
 JAMBOR, WILLIAM P, 60 90-108, 109-120, 121-130, 67 354-365, 366-375  
 JAMES, E F, 71 321-323  
 JAMES, H A, 79 541  
 JAMES, LANN A, 63 275-294  
 JAMPS, VETILE D, 65 722-734  
 JAMESON, A GREGORY, 80 510-521  
 JAMESON, ELIZABETH L, 71 272-279  
 JANNER, JOSÉ L, 67 132-153, 70 1099-1101  
 JANICKI, BERNARD W, 79 244-245  
 JANN, GREGORY J, 71 260-265, 266-271  
 JARROLD, THOMAS, 70 509-517  
 JEFFERIES, MILDRED B, 77 350-355, 79 669-671  
 JEKER, K, 79 351-356  
 JENKINS, BARBARA E, 68 264-269  
 JENKINS, DANIEL E, 64 170-181, 68 541-547, 727-733, 74 417-427, 468-470  
 JENKINS, JOHN T, 72 12-34  
 JENNINGS, A R, 61 399-406  
 JENNINGS, J C, 62 475-480  
 JENNINGS, PAMELA A, 72 171-195  
 JENNINGS, WILMA, 75 1003-1006  
 JENSEN, K A, 70 402-412  
 JENSEN, N KENNETH, 74 367-375  
 JOHNSON, LYNN, 68 229-237, 69 1054-1056  
 JOHNSON, ALAN J, 76 1-21  
 JOHNSON, BERKLEY H, 61 578-581  
 JOHNSON, HENRY P, 75 139-144  
 JOHNSON, JANET J, 76 247-255  
 JOHNSON, JOAN M, 77 623-643  
 JOHNSON, JOHN E, JR, 66 497-500, 72 91-97  
 JOHNSON, J RICHARD, 70 623-636, 72 825-832  
 JOHNSON, LINDEN E, 67 299-321  
 JOHNSON, MAURINE P, 69 287-296, 980-990  
 JOHNSON, PEGGY M, 72 390-392, 863-865  
 JOHNSON, PHILIP C, 78 391-398  
 JOHNSON, RICHARD P, 59 656-663  
 JOHNSON, ROBERT S, 68 177-187, 70 296-303

JOHNSON, WILLIAM H, 73 99-109  
 JOHNSTON, DALE GORDON, 75 319-325  
 JOHNSTON, JOSEPH A, 74 (Supplement, August 173-182)  
 JOHNSTON, R N, 70 442-452, 78 932-933  
 JOHNSTON, WENDIE E, 69 991-1001  
 JOINER, C L, 71 302-304  
 JOLLI, PAUL N, 60 589-603  
 JONES, AUDREY P, 70 266-273  
 JONES, EDNA M, 61 387-398, 60 533-534, 71 766  
 JONTS, FRANCIS S, 68 657-677  
 JONES, JOHN C, 73 690-703  
 JONES, JULIA M, 73 229-238  
 JONES, MERRIAM J, 68 425-438, 439-443, 444-450  
 JONES, OSWALD R, 60 514-519  
 JONES, PERON O, 68 541-547, 74 417-427, 468-470  
 JONES, RALPH, JR, 63 672-673  
 JONES, ROBERT KNAPP, 74 802-806  
 JONES, RUSSELL S, 61 826-834, 63 381-398  
 JONES, WARREN, 63 459-469, 71 319  
 JONES, WILLIAM WILEY, 60 45-50  
 JORDAHL, CLARENCE, 75 659-666, 77 539-542, 80 431-433  
 JUAREZ, WILLIAM J, 76 468-479  
 JUHL, J W, 74 388-399  
 JUDGE, J M, 60 62-77

## K

KAHN, M T, 76 892-895  
 KAHN, MARCEL, 61 887-891  
 KALISH, CATHERINE, 65 187-193, 67 497-502  
 KALLQVIST, IVAR, 61 621-642, 64 430-441, 69 968-979, 73 40-51  
 KAMENER, ROBERT, 77 209-220  
 KANAI, KOOMI, 80 753-756  
 KANE, J H, 63 1-3  
 KANNER, O, 76 669-670  
 KANTOR, MILTON, 78 274-281, 524-535  
 KAPRAL, FRANK A, 78 712-724  
 KAPUR, VISHWA N, 80 269-273  
 KARA, CHARLES, 76 789-798  
 KARLSON, ALFRED G, 62 149-155, 62 345-352, 63 36-43, 427-433, 66 477-485, 722-731, 67 341-353, 68 75-81, 575-582, 70 531-532, 75 266-279, 78 753-759  
 KARNOFSKY, DAVID A, 69 957-962  
 KARNOSH, LOUIS J, 62 428-433  
 KARNOVSKY, MANFRED L, 71 609-616  
 KARNS, JAMES R, 79 746-755  
 KARPINOS, BERNARD D, 80 795-805  
 KASS, IRVING, 65 316-324, 74 796-797, 80 1-5  
 KASTL, WILLIAM H, 66 522-533  
 KASUGA, KAZUMI, 68 157-164, 799-802  
 KÁTÓ, LÁSZLÓ, 73 442-443, 75 684-687  
 KATO, MASAHIKO, 77 482-491, 80 240-248, 535-542  
 KATSUMURA, TATSUKI, 79 232-237  
 KATZ, EDWARD, 60 78-89



- KATZ, HARRY L, 61 835-844, 65 455-464, 589-595  
 KATZ, JULIUS, 61 51-56, 66 651-665, 67 279-285,  
 70 32-48, 73 31-39, 74 968-971, 862-870  
 KATZ, SOL, 68 760-770, 70 881-891, 74 106-111,  
 80 590-593  
 KAUFMAN, C J, 66 605-614  
 KAUFMAN, GERALD, 68 24-30  
 KAUFMAN, JEROME E, 70 689-700  
 KAUFMAN, KYESL K, 66 244-245, 79 525  
 KAWAI, KEIZO, 79 232-237  
 KAZLOWSKI, JOSEPH P, 73 266-275  
 KEE, JOHN L, JR, 76 970-982  
 KEEN, E N, 59 511-518  
 KELLER, ROBERT, 76 697-702  
 KELLEY, WINFIELD O, 65 83-87  
 KELLY, JACQUES M, 65 484-485  
 KELLY, MARGARET C, 68 564-574  
 KELLY, RUBY G, 61 269, 67 286-291, 68 583-593  
 KENDIG, EDWIN L, JR, 61 747-750, 70 161-165,  
 73 99-109, 74 149-151, 77 418-422  
 KENDIG, ISABELLE V, 73 438-441  
 KENNEDY, B R, 61 443-464  
 KENNEDY, H E, 77 802-814, 78 799-801  
 KENNEDY, R S, 68 400-410  
 KENNEY, MICHAEL, 70 149-154, 72 390-392, 863-865  
 KENT, DONALD C, 80 806-824  
 KENT, EDWARD M, 60 699-705, 73 134-138  
 KENT, G, 77 931-939  
 KERGIN, FREDERICK G, 66 732-743  
 KERNAN, PHILIP, 73 620-636, 75 442-460  
 KESCHNER, HAROLD W, 68 136-143  
 KESSLER, BRUCE J, 63 202-209  
 KHAN, I, 79 474-483  
 KHUNDKAR, A M, 78 117-120  
 KILBOURNE, PHILIP C, 60 564-575  
 KILBURN, KAYE H, 80 441-442  
 KING, COLEMAN T, 75 199-222  
 KING, DONALD S, 60 536-538  
 KING, EDWARD J, 80 895-901  
 KING, ERNEST Q, 60 564-575  
 KINGSLEY, GEORGE R, 77 181-183  
 KINNEAR, A A, 59 511-518  
 KINSELL, LAURANCE W, 66 542-547  
 KINSELLA, T J, 59 113-127  
 KIRBY, WILLIAM M M, 60 343-353, 64 71-76,  
 69 625-630, 80 716-723  
 KIRCHHEIMER, WALDEMAR F, 62 481-483, 64  
 516-519, 66 486-496, 758-761, 68 629-630, 70  
 665-671, 920-921, 71 743-751  
 KIRK, DANIEL L, 74 7-14  
 KIRMAN, DAVID, 77 184-188  
 KIRMSE, THOMAS W, 61 159-170  
 KIRSCHNER, PAUL A, 61 465-473  
 KIRSH, D, 72 345-355  
 KIRSHNER, J J, 78 474-477  
 KISER, J S, 65 511-518  
 KITAZAWA, YUKIO, 74 155-157, 79 329-338  
 KITCHELL, CYNTHIA L, 75 1003-1006  
 KITTLE, C FREDERICK, 77 387-399  
 KLASSEN, KARL P, 66 699-721, 74 874-884, 77  
 62-72  
 KLEIN, G C, 60 621-627, 63 459-469  
 KLEIN, SARAH, 68 290-291, 69 1022-1028, 74 428-  
 437  
 KLIEMAN, ALBERT M, 63 441-448, 672-673, 674-678  
 KLOPFENSTEIN, MORRIS D, 69 451-454, 70 533-  
 534, 71 766  
 KLOPSTOCK, ROBERT, 60 273-287, 73 831-852  
 KNATSI, GEORGES, 66 567-577  
 KNIAZUK, MICHAEL, 68 212-219  
 KNIGHT, RALPH A, 77 983-989, 78 944-948, 80  
 264-266  
 KNIGHT, VERNON, 77 134-145, 80 12-18, 443-444  
 KNOEPP, LOUIS F, 66 522-533  
 KNOWLES, ROBERT G, 75 618-623, 624-629  
 KNOX, ROBERT, 73 726-734  
 KNUDSON, JACK R, 61 809-825  
 KNUDTSON, KENNETH P, 71 280-290  
 KOCH, MARIE L, 73 773-775, 77 356-358  
 KOCH-WESER, DIETER, 67 490-496, 70 784-792,  
 71 556-565, 75 71-82  
 KOERBER, W L, 68 284-285  
 KOEVOET, A O, 75 843-845  
 KOLMER, JOHN A, 64 102-112  
 KONNO, KIYOSHI, 75 529-537, 77 669-674, 675-680,  
 79 810-812  
 KONOPKA, E A, 70 121-129, 130-138, 77 694-702,  
 703-711  
 KONTERWITZ, H, 69 1057-1058  
 KONVALER, BENJAMIN E, 78 906-915  
 KORY, ROSS C, 77 729-736  
 KOTT, THADDEUS J, 63 487-489, 65 194-200  
 KOURTI, H, 74 (Supplement, August 197-208)  
 KOVITZ, C, 70 465-475, 641-664  
 KRAFT, JOSEPH R, 59 259-269  
 KRAHL, VERNON E, 80 (Supplement, July 24-40,  
 158-167)  
 KRASNITZ, ALEXANDER, 68 249-252  
 KRASNOW, IRVING, 71 361-370, 76 435-450, 451-467,  
 77 1030-1031  
 KRAUS, WILLIAM, 79 731-737  
 KREHL, W, 76 692-696  
 KREININ, SIDNEY, 59 650-655  
 KREIS, B, 80 85-88  
 KREISEL, HERBERT, 67 286-291, 292-298  
 KRESS, MILTON B, 80 (Supplement, July 194-202)  
 KROHN, EDWARD F, 70 376, 74 808-809  
 KROSS, ISIDOR, 61 431-435  
 KRUEGER, ERICH, 62 654-666  
 KRUEGER, VICTOR R, 76 64-75  
 KRUGER-THIEMER, ECKEHARD, 77 364-367  
 KU, HSIEN-CHIH, 60 483-486  
 KUBALA, EUGEN, 78 949-951  
 KUBICA, G P, 73 529-538  
 KUHN, D M, 69 464-468  
 KULISH, M, 60 223-227, 65 635-636

- KUNA, MARTIN, 64 577-578  
 KUNOFSKY, SOLOMON, 70 32-48, 73 31-39, 74 968-971, 78 862-870  
 KURTZKE, JOHN F, 70 577-592  
 KURUCZ, JANOS, 76 789-798  
 KURUNG, JOSEPH M, 65 181-186, 66 578-587, 76 671-674, 675-678, 679-689  
 KURZMANN, RUDOLF, 75 529-537, 77 669-674, 675-680  
 KUSCHINSKI, HERTA, 63 213-219  
 KUSHNER, DANIEL S, 76 103-107, 108-122, 80 434-437  
 KUSUNOSE, MASAMICHI, 80 240-248  
 KWIEK, STANISLAW, 80 257-258
- L**
- LACK, CHARLES H, 73 362-377, 378-389, 74 (Supplement, August 124-133)  
 LAFF, HERMAN I, 74 (Supplement, August 267-277)  
 LAFORET, EUGENE G, 77 716-718  
 LAING, W A R, 71 201-219  
 LAMBERT, H P, 80 648-658  
 LAMBIOTTE, LOUIS O, 59 289-310  
 LAMOTTE, IRENE F, 80 181-187  
 LANDIS, FRANCIS B, 80 249-254  
 LANE, JAMES J, JR, 73 795-804  
 LANG, LEONARD P, 59 270-288, 61 201-225  
 LANGMUIR, ALEXANDER D, 64 461-467  
 LANGTON, GERTRUDE K, 62 190-208  
 LARKIN, JOHN C, JR, 63 116-118, 69 443-450, 72 667-674, 843-845, 75 667-669, 78 135-137  
 LAROS, C D, 78 563-569  
 LARSEN, AUBREY B, 68 425-438, 439-443, 444-450, 77 177-180, 712-715  
 LARSEN, D H, 74 284-288  
 LARSH, HOWARD W, 75 938-948  
 LARSON, FRANK C, 70 102-108  
 LARSON, L M, 59 113-127  
 LASCHE, EUNICE M, 80 188-199  
 LATTIMER, JOHN K, 61 518-524, 66 744-749, 67 604-612, 69 618-624, 70 149-154, 76 909-911  
 LAUBACH, C A, JR, 60 1-14  
 LAUENER, H, 79 351-356, 80 26-37  
 LAURIE, J H, 62 331-332  
 LAVALLEE, A, 68 199-207  
 LAWRENCE, CARL A, 79 374-377  
 LAWRENCE, L THEODORE, 80 575-581  
 LAWRENCE, MONTAGUE S, 72 801-809  
 LAWRENCE, SANFORD H, 77 181-183  
 LAWSON, JOHN F, 59 687-691  
 LAWTON, ALFRED H, 80 915-918  
 LEACH, RONALD L, 68 321-341, 342-371  
 LECHÉVALIER, HUBERT A, 67 261-264  
 LEDERER, E, 67 853-858  
 LEE, HENRY F, 61 738-741, 66 623-625  
 LEE, J ROBERT, 69 625-630  
 LEE, S C, 72 356-366  
 LEE, SEUNG HOON, 74 572-580, 76 1106-1109  
 LEECH, F B, 69 806-817  
 LEES, A W, 68 400-410, 78 769-772  
 LEES, T M, 63 1-3  
 LEES, WILLIAM M, 61 648-661, 78 822-831  
 LEFEBER, EDWARD J, 61 247-256  
 LEFTWICH, CHARLES I, 77 737-748  
 LEGOLVAN, P C, 79 119-133  
 LEHAN, PATRICK H, 75 938-948  
 LEHMAN, J STAUFFER, 69 657-672  
 LEIFHEIT, HOWARD C, 79 344-350  
 LEIFSON, EINAR, 75 148-152  
 LEIGHNINGER, DAVID S, 71 904-924  
 LEINER, GEORGE C, 61 868-874, 63 325-331, 65 465-476, 76 320-321, 80 902-903  
 LEISE, J M, 78 111-116  
 LEITES, VERA, 80 89-94  
 LEKOU, S, 76 263-271  
 LEMAISTRE, CHARLES, 64 295-306  
 LEMEUR, G, 79 6-18  
 LEMONDE, PAUL, 71 319-321  
 LENERT, TULITA F, 60 808-810, 63 1-3, 17-24, 434-440, 65 754-774, 68 292-294, 70 191-218, 527-530, 71 457-458, 72 367-372, 386-389, 846-850, 76 1031-1048, 78 934-938, 939-943, 80 274-276  
 LENNOX, R H, 74 (Supplement, August 160-168)  
 LEONARD, ALAN J, 68 382-392  
 LEONARDI, A, 80 110-111  
 LEPINE, LOUIS T, 73 438-441  
 LEPPER, MARK H, 69 192-204  
 LERNER, ERNEST N, 80 188-199  
 LESTER, CHARLES W, 64 691-694, 73 229-238, 78 399-402  
 LESTER, WILLIAM, 74 121-127, 77 462-472  
 LEUALLEN, EDMUND C, 72 783-801  
 LEVIN, NILS, 72 513-526  
 LEVINE, I, 69 1057-1058  
 LEVINE, MACY I, 59 701-706, 67 535-537  
 LEVINE, MILTON I, 62 118-119  
 LEVINF, MORTON, 75 517-518, 77 501-505  
 LEVY, DAVID, 79 666-668, 80 587-589  
 LEVY, F M, 79 484-491  
 LEVY, RICHARD S, 79 152-179, 180-203  
 LEW, JOON, 74 152  
 LEWIN, EDWARD, 71 447-451, 732-741  
 LEWIS, ALBERT G, JR, 80 188-199  
 LEWIS, EDWARD C, II, 74 438-440  
 LEWIS, GEORGE T, 66 378-380  
 LEWIS, W G, 61 881-882  
 LEWIS, WILLIAM C, 70 892-898, 71 419-428, 72 633-646, 73 338-350, 74 964-967, 77 311-322  
 LEWKOWICZ, STEPHANIE, 74 15-28  
 LIACACOS, D, 74 (Supplement, August 197-208), 76 263-271, 79 522-524  
 LIBERMANN, DAVID, 79 1-5  
 LICHTENSTEIN, HERMAN, 69 837-810

- LICHTENSTEIN, LOUIS, 60 249-257  
 LICHTENSTEIN, MEYER R , 60 576-588, 64 77-80,  
 66 161-174, 68 229-237, 69 247-260, 74 961-963  
 LIEBERMAN, J E , 59 438-448  
 LIEBOW, AVERILL A , 80 (Supplement, July 67-91)  
 LIVES, BARNEY J , 79 606-611  
 LIN, T K , 77 387-399  
 LINCOLN, ARTHUR F , 75 999-1003, 77 536-538  
 LINCOLN, EDITH M , 61 159-170, 64 499-507, 66  
 63-76, 67 732-754, 69 682-689, 73 940-943, 74  
 15-28, (Supplement, August 246-255), 75  
 594-600, 76 588-600, 77 39-61, 271-289, 79  
 31-40  
 LINCOLN, N STANLEY, 62 572-581, 66 16-27, 68  
 238-248, 70 15-31, 71 193-200, 519-528, 72  
 242-244, 77 413-417  
 LINDEN, IRWIN H , 69 116-120  
 LINDGREN, INGA, 80 (Supplement, July 185-193)  
 LINDH, HOWARD, 65 511-518  
 LINDSAY, STUART, 66 77-85  
 LINDSEY, ERICKA, 73 581-585  
 LINDSKOG, GUSTAF E , 63 579-586, 70 155-160  
 LINEBERRY, WILLIAM T , JR , 61 426-430  
 LINELL, MICHAEL A , 74 410-416, 76 636-642  
 LINKER, MATTHEW , 62 441-445  
 LINN, RICHARD H , 70 1020-1029, 72 663-666,  
 74 464-467, 622-623, 79 251-252, 531-532  
 LISA, JAMES R , 63 202-209  
 LITTLE, MARSHALL S , 75 145-147, 76 906-908  
 LITZENBERGER, WILLARD L , 69 443-450  
 LIU, KUANG-YUAN, 60 483-486  
 LIVING, DOROTHY G , 70 637-640, 72 756-782  
 LOCKE, BEN Z , 70 32-48, 73 31-39  
 LOCKHART, ELIZABETH A , 80 95-99  
 LOGAN, P L , 71 830-840  
 LONG, ESMOND R , 59 481-493, 60 527-531, 62  
 (Supplement, July 3-12), 63 355-359, 64 381-  
 393, 65 494-503, 69 631-633, 70 383-390, 71  
 609-616, 75 852-855, 78 499-511  
 LOOSLI, CLAYTON G , 80 (Supplement, July 5-20)  
 LÓPEZ MAJANO, VICENTE, 72 537-538  
 LORBER, JOHN, 69 13-25, 78 38-61, 101-105  
 LORENZ, THOMAS H , 66 449-456, 70 892-898,  
 71 419-428, 72 633-646, 73 338-350  
 LORRIMAN, GERARD, 79 756-763  
 LOTT, WILLIAM A , 65 357-364, 67 354-365, 366-375  
 LOUDON, R G , 77 623-643  
 LOVEJOY, FRANK W , JR , 59 364-369, 62.29-44  
 LOVELOCK, FRANCIS J , 72 390-392  
 LOW, EUGENE, 79 612-621  
 LOWE, E P , 70 498-503  
 LOWELL, ANTHONY M , 72 419-452  
 LOWELL, FRANCIS C , 80 (Supplement, July  
 181-183)  
 LOWELL, JAMES R , 78 391-398  
 LOWELL, LAWRENCE M , 68 885-901  
 LOWENSTEIN, BERNARD, 72 373-380, 74 977  
 LOWRI, HOPE, 60 51-61  
 LU, F C , 68 199-207  
 LU, SUNG-NIEN, 62 360-373  
 LUBING, HAROLD N , 68 458-461  
 LUCAS, E H , 62 475-480  
 LUFT, ULRICH C , 72 465-478  
 LUKAS, DANIEL S , 64 279-294  
 LULL, GEORGE F , JR , 79 641-651  
 LUNN, JOSEPH, 79 72-77  
 LUPINI, BELARDINO, 79 307-314  
 LURIDIANA, NIVEO, 73 785-786  
 LURIE, MAX B , 59 1-9, 168-185, 186-197, 198-218,  
 61 765-797, 67 265-266, 69 1059-1060, 72 297-  
 329, 73 434-437, 79 152-179, 180-203  
 LUTZ, W , 77 400-412  
 LYNCH, HELEN P , 67 106-107, 69 307-308, 77  
 1023-1025  
 LYNCH, WILLIAM J , 68 229-237  
 LYON, RICHARD H , 76 247-255, 79 518-521  
 LYONS, HAROLD A , 64 327-352, 71 635-667  
 LYTCHOTT, GEORGE I , 73 940-943, 75 135-138
- ## M
- MA, JOHN, 74 457-461  
 MA, Y Y , 59 519-538  
 McALISTER, ELIZABETH, 79 669-671  
 McAULIFFE, WILLIAM J , 60 524-526  
 McCLELLAN, MARVIN, 70 1064-1082  
 McCLEMENT, JOHN H , 63 231-251, 64 583-601,  
 67 154-172  
 McCLOSEY, E T , 59 438-448  
 McCORD, DON L , 78 21-37  
 McCORMACK, LAWRENCE J , 71 668-675  
 McCORMICK, GEORGES F , 68 760-770, 70 881-891  
 McCoy, HERBERT T , 62 227, 353-359  
 McCuiston, C FRED, 76 480-490  
 McCune, ROBERT M , JR , 69 319-333, 70 743-747,  
 72 851-855, 74 471-473, 572-580, (Supplement,  
 August 100-108), 75 659-666, 76 1100-1105,  
 1106-1109  
 MacCurdy, JOE M , 66 497-500  
 MacDERMOT, P N , 76 832-851  
 McDermott, WALSH, 61 145-157, 63 49-61, 65 429-  
 442, 66 391-415, 68 791-793, 69 319-333, 1029-  
 1036, 70 228-265, 743-747, 748-754, 71 316-317,  
 72 851-855, 74 572-580, (Supplement, August  
 100-108), 75 659-666, 76 1100-1105, 1106-1109,  
 77 539-542, 80 431-433  
 McDougall, J B , 64 218-222  
 McDowell, CHISHOLM, 69 612-617  
 McDowell, MARION, 62 29-44  
 McElroy, ROBERT J , 69 604-611  
 McGETTIGAN, MARIE T , 70 71-90  
 McGREGOR, MAURICE, 77 209-220, 78 692-696  
 Macias, JOSÉ DE J , 79 265-272  
 MacIntyre, SYLVIA B , 80 915-918  
 Mack, IRVING, 64 50-63

- MACKANESS, G B , 66 125-133, 67 322-340, 69 479-491, 495-504, 690-704, 74 718-728
- McKEE, A P , 72 687-689
- McKEE, CLARA M , 60 90-108, 109-120, 121-130, 63 556-567
- McKENNIS, HERBERT, JR , 73 956-959
- McKENZIE, DORIS, 65 511-518
- MACKEPRANG, BFNT, 76 914-915
- McKIM, ANSON, 66 457-476
- McKINNEY, RUTH A , 77 1019-1022
- McKNIGHT, HERBERT V , 70 701-703
- McKUSICK, VICTOR A , 72 12-34
- McLAREN, LEROY C , 71 260-265, 266-271
- MACLEAN, K S , 71 302-304
- McLEAN, KENNETH H , 80(Supplement, July 58-64)
- McLEAN, ROSS, L , 75 420-431, 514-516
- McLELLAN, FRED C , 69 618-624
- MacLEOD, H M , 68 400-410
- McMILLEN, SHIRLEY, 76 103-107, 108-122, 80 434-437
- MACNAMARA, J , 70 274-284
- McPHEE, HARRY R , 61 138-144
- MACQUIGG, RODGER E , 72 465-478
- MACRAE, D M , 61 355-368
- McROBERTS, CARRIE C , 71 762-764
- MAGNUS, KNUT, 72 126-128, 74 297-303
- MAGNUSSEN, MOGENS, 72 126-128, 74 297-303
- MAHADI, STEPHEN C F , 68 238-248, 72 242-244, 73 776-778
- MAHER, JOHN R , 75 517-518, 999-1002, 76 852-861, 77 501-505
- MAHEUX, P , 71 867-876
- MAHON, HUGH W , 61 543-555
- MAIDEN, SYDNER D , 62 549-554
- MAIER, HERBERT C , 63 220-226, 65 206-209
- MAILLARD, EDGAR R , 64 675-681, 66 762-764
- MAIS, EDWARD L , 79 307-314
- MAISEL, BERNARD, 78 623-631
- MAJOR, JAMES W , 61 346-352
- MAJUMDAR, NIRMAL K , 75 644-647
- MALIN, RUTH B , 60 439-447, 448-454
- MALKIEL, SAUL, 68 629-630
- MALLMANN, W L , 71 382-389
- MALONE, LUKE, 65 511-518
- MANDEL, W , 74 796-797
- MANDELBAUM, THEODORE, 66 594-600
- MANKIEWICZ, EDITH, 75 836-840
- MANTEN, A , 74 633-637, 958-960
- MANTZ, HERBERT L , 69 227-233, 234-240
- MARCHD, J , 79 6-18
- MARCHESE, VINCENT, 66 699-721
- MARCUS, STANLEY, 75 849-850, 77 983-989, 80 264-266
- MARDIS, RICHARD E , 63 295-311
- MARESH, F , 59 391-401
- MARGOLIS, JACK, 75 828-832
- MARIETTE, E S , 59 113-127
- MARION, ARTHUR J , 80 59-64
- MARK, DONALD D , 79 440-449
- MARK, HARRIS J , 68 286-289, 73 593-596
- MARKAROGU, L , 66 100-103
- MARKS, ASHER, 74 317-342
- MARKS, J , 71 566-572
- MARKS, ROBERT H , 78 871-883
- MARMION, THOMAS, 80 278
- MAROLLA, MICHAEL M , 71 295-298
- MARRANGONI, ALBERT G , 72 257-267
- MARSH, K , 71 302-304
- MARSHAE, ALFRED, 62 333, 65 75-82
- MARSHALL, EDWARD E , 63 103-118
- MARTIN, C J , 73 330-337, 77 260-270
- MARTIN, FRANK E , 66 509-521
- MARTIN, G E , 66 501
- MARTIN, JOSEPHINE D , 66 63-76
- MARTINEAU, PERRY C , 66 151-160
- MASCHER, WILLI, 63 501-525, 64 469-470
- MASON, CARL B , 80 6-11
- MASON, DANIEL, 69 657-672
- MASON, RICHARD C , 74 972-976
- MASON, W ROY, 66 345-350
- MATHEWSON, JOHN A , 74 142-144
- MATHISEN, ARNE K , 65 443-450
- MATSUNAGA, KIYOTERU, 77 482-491, 80 240-248, 535-542
- MATTARN, C F T , 65 48-63
- MATTHIENSEN, DON E , 69 829-836
- MATTILL, P M , 59 113-127
- MATTINSON, MARJORIE W , 65 572-588, 69 92-103
- MATTSON, S -B , 78 536-546
- MAUDERLI, WALTER, 77 375-386
- MAUSER, MARIE, 80 274-276
- MAYER, EDGAR, 62(Supplement, July 80-89)
- MAYER, EDMUND, 69 419-442
- MAYER, R L , 70 121-129, 130-138, 77 694-702, 703-711
- MAYER, S W , 71 889-891
- MAYOCK, ROBERT L , 71 529-543
- MEADE, GORDON M , 59 429-437, 60 541-546, 65 754-758
- MEADE, RICHARD H , JR , 60 683-698
- MEADOR, ROBERT S , 74 638-640, 75 53-61, 76 47-63
- MEADOW, PAULINE M , 73 726-734
- MEANS, J A , 63 1-3
- MEDLAR, EDGAR M , 62 101-108, 63 449-458, 66 381-382, 71(Supplement, March 1-244)
- MEIER, PAUL, 62 190-208, 65 201-205, (Supplement, January 1-50)
- MEIER, WALTER A , 69 543-553
- MEINDERSMA, MARTIN S , 80 915-918
- MEISSNER, WILLIAM A , 60 406-418
- MELANIDES, G , 72 859-862
- MELICK, D W , 62 116-117, 77 17-21
- MELLETT, SUSAN J , 69 824-828
- MELVIN, IRENE, 63 459-469, 78 83-92, 799-801

- MENDENHALL, JOHN T , 72 569-576  
 MERKAL, RICHARD S , 77 177-180, 712-715  
 MERRILL, DUANE L , 77 561-592  
 MERTENS, ANTON, 61 20-38  
 MEYER, ANDREW H , 66 542-547  
 MEYER, B W , 73 690-703  
 MEYER, JOHANNES, 70 402-412  
 MEYER, K F , 74 566-571  
 MEYER, MARYETHEL, 71 765-766  
 MEYERS, CHARLES E , 71 371-381  
 MEYERS, HARVEY I , 74 590-596  
 MICHAEL, MAX, 62 403-407  
 MICK, FELIX, 64 453-460  
 MIDDLEBROOK, GARDNER, 62 223-226, 65 765-767,  
     69 471-472, 70 465-475, 504-508, 641-664, 922,  
     1030-1041, 1102-1103, 71 390-405, 441-446,  
     765-766, 72 653-658, 693, 73 944-955, 74 42-49,  
     75 155-156, 656-658, 80 1-5, 587-589  
 MIDDLETON, JOHN W , 62 439-440  
 MIETZSCH, FRITZ, 61 1-7  
 MIHALY, JOHN P , 69 673-681, 79 307-314  
 MIKI, KATSUJI, 77 482-491, 80 240-248, 535-542  
 MIKOL, EDWARD X , 66 16-27  
 MILGRAM, LILLIAN, 75 897-911  
 MILLER, BENJAMIN F , 63 492  
 MILLER, D V , 74 178-187  
 MILLER, DONALD B , 77 848-857, 80 825-832  
 MILLER, DOROTHY E , 60 189-205  
 MILLER, EARL R , 64 225-248, 249-255  
 MILLER, ELIZABETH E , 73 547-562  
 MILLER, FRANK L , 66 534-541, 69 58-64  
 MILLER, IRVING L , 73 716-725  
 MILLER, JAMES N , 68 31-41  
 MILLER, JOSEPH B , 62 91-98  
 MILLER, JOSEPH M , 60 212-222  
 MILLER, RUSSELL, JR , 70 1053-1063  
 MILLER, TRACY B , 75 999-1002  
 MILLER, WALTER T , 77 260-270  
 MILLER, WILLIAM F , 71 693-703, 79 315-322  
 MILLER, WILLIAM M , 74 638-640  
 MILLS, CRETYL C , 75 420-431  
 MILLS, LEWIS C , 68 541-547  
 MILLS, WALDO H , 71 280-290  
 MINARD, EUGENE W , 73 882-891  
 MINKIN, ALBERT, 70 728-733  
 MINOR, GEORGE R , 73 79-98  
 MISCALL, LAURENCE, 73 831-852  
 MISENER, F J , 79 468-473  
 MITCHELL, MILDRED B , 79 533-536  
 MITCHELL, ROGER S , 60 168-182, 183-188, 61 809-  
     825, 64 1-20, 21-26, 27-40, 227-140, 141-150,  
     151-158, 67 401-420, 421-431, 68 863-873,  
     69 963-967, 71 602-603, 72 487-501, 502-512,  
     653-658, 75 180-298, 346-347, 76 152-158, 491-  
     496, 508-509, 80 108-110, 207-215, (Supple-  
     ment, July 2-4, 213)  
 MITCHISON, D A , 69 640-644, 74 (Supplement,  
     August 109-116)
- MIURA, KOJI, 76 298-300  
 MIZUNO, DENJI, 75 488-494  
 MIZZONI, R H , 77 703-711  
 MOEN, CHESTER W , 60 1-14  
 MOLD, JAMES D , 63 4-6  
 MOLLOV, MOLLIE, 63 487-489, 65 194-200  
 MOLNAR, LADISLAO, 66 90-94  
 MOLOMUT, NORMAN, 62 337-344, 67 101-102  
 MOLTHAN, LYNDALL, 71 220-227  
 MONROE, JAMES, 62 572-581, 71 193-200, 73 776-  
     778, 77 413-417  
 MONTALBINE, VINCENT, 76 643-659, 78 454-461,  
     570-575, 79 66-71  
 MONTES, MARIO, 75 343-344, 79 362-370  
 MOORE, FREDERICK J , 75 618-623, 624-629, 76 752-  
     760, 80 216-222  
 MOORE, JANE, 78 576-582  
 MOORE, T , 80 223-231  
 MOORMAN, LEWIS J , 61 586-591, 62 446-448  
 MORALES, SOLEDAD M , 75 594-600  
 MORAVEC, MARGARET, 63 679-693  
 MORGAN, RUSSELL H , 64 313-317  
 MORGANTE, O , 76 832-851  
 MORGENSTERN, PHILIP, 59 53-67, 60 25-31  
 MORRIS, CHARLES S , 78 274-281, 524-535, 79 512-  
     517, 577-590  
 MORRIS, GWENDOLYN L , 68 791-795  
 MORRISSEY, JOHN F , 80 855-865  
 MORSE, DRYDEN P , 75 865-884  
 MORSE, W C , 69 464-468, 72 840-842  
 MORTON, DAVID E , 73 351-361  
 MORTON, J W , 79 474-483  
 MORTON, M E , 71 889-891  
 MOSELEY, CHARLES H , 59 481-493  
 MOSER, KENNETH M , 76 480-490  
 MOSHIN, JEAN R , 68 31-41, 594-602, 70 344-348  
 MOTAMEDI, GHASSEM, 80 587-589  
 MOTIWALE, ACHYUT G , 77 168-171  
 MOTLEY, HURLEY L , 59 270-288, 61 201-225,  
     76 601-615, 77 737-748  
 MOULÓN, MARIO, 73 61-71  
 MOUNT, FRANK W , 66 632-635, 67 108-113, 539-  
     543, 68 264-269, 70 521-526, 80 371-387  
 MOUSA, A H , 79 119-133  
 MOYER, JOHN H , 61 131-137, 299-322, 63 176-193,  
     255-274, 399-416, 64 659-668, 68 541-547  
 MOYER, RALPH E , 61 875-880, 62 563-571, 64 41-  
     49, 70 413-422, 924, 76 1097-1099, 79 90-93  
 MUCHMORE, HAROLD G , 80 267-268  
 MUDD, STUART, 67 59-73, 68 625-628  
 MUELLER, EDWIN E , 59 391-401, 60 794-800,  
     67 292-298, 70 518-520, 533-534, 71 766  
 MUELLER, EUGENE, 80 (Supplement, July 194-  
     202)  
 MUENDEL, HAROLD J , 67 232-246  
 MULLIN, EDWARD W , 67 652-656  
 MULVIHILL, D A , 66 605-614  
 MUNROE, W G C , 65 523-546

MURPHY, JAMES D , 63 81-81, 66 136-118, 67 22-28,  
68 535-510, 71 892-893, 73 191-218  
MURPHY, MARION L , 72 690-692  
MURRAY, FRANCIS I , 80 371-387  
MUSCHFELNHEIM, CARL , 60 110-112, 63 19-61, 65 129-  
142, 66 391-115, 68 791-793, 796-798, 69 319-  
333, 813-851, 70 228-265, 713-717, 71 316-317,  
72 1-11, 851-855, 75 659-666, 77 539-512,  
80 431-433  
MUSSEK, MARC J , 66 419-456  
MYERS, I ARTHUR, 71 885-888, 73 620-636, 75 412-  
460, 79 19-30, 80 100-107  
MYRIK, QLENTIN N , 64 669-671, 67 217-231,  
68 564-574, 69 406-418, 73 559-592, 78 93-100,  
79 339-343

## N

NACMAN, MARTIN, 80 111-112  
NAGELF, CHARLES F , 64 564-571  
NAGAH, A M EL, 79 119-133  
NAHAS, HECTOR C , 64 620-629  
NAIR, K G S , 75 553-575  
NAKAJIMA, MICHIO, 78 881-898  
NAKAMURA, SHIGERU, 75 99-101  
NAKANO, AKINORI, 79 232-237  
NARITA, MITSUNORI, 69 297-299  
NATHAN, ARTHUR, 80 424-425  
NATIONAL TUBERCULOSIS ASSOCIATION—INTER-  
ANS ADMINISTRATION, 72 866-868  
NAYER, H R , 62 654-666, 67 509-513  
NAYLOR FOOTF, A W C , 79 374-377  
NÈGRE, L , 68 467-470, 71 807-808  
NEIMAN, IRWIN S , 59 102-105  
NELSON, CLARENCE, 60 15-50  
NELSON, SOL S , 68 127-135  
NELSON, WALDO E , 71 (Supplement, August 256-  
266)  
NEMEC, F C , 59 113-127  
NEMIR, ROSA LEE, 62 618-631, 66 63-76  
NEPTUNE, WILFORD B , 61 185-192, 63 710-713,  
64 391-407  
NETSKY, MARTIN G , 62 586-593  
NETZER, SOLOMON, 63 62-66  
NEUMANN, GERTRUDE, 77 245-259  
NEVILLE, JOHN F , JR , 73 134-138  
NEWELL, R R , 69 556-584  
NEWMAN, LOUIS B , 71 272-279  
NEWMAN, MELVIN M , 71 676-692, 80 806-824  
NEWMAN, ROBERT W , 79 204-211  
NEWTON, J K , 63 476-479  
NICHOLS, GEORGE P , 76 1016-1030  
NICHOLS, NORMAN J , 80 833-844, 895-901  
NICKERSON, GRANVILLE H , 76 832-851, 78 485  
NIMTZ, HERMAN J , 70 430-441  
NINOS, GEORGE S , 73 434-437  
NISSIN MEYER, SVEN, 66 292-313, 69 383-395  
NODA, YO, 78 121-126, 79 371-373

NOLAN, RICHARD B , 73 831-852  
NOIL, HANS, 67 828-852  
NORMAN, JAMES O , 71 762-764  
NORMAN, JANE W , 65 692-708  
NORVITT, LEMBIT, 67 258-260  
NOUFLAND, HENRIETTE, 72 330-339, 80 326-339  
NOZZOLI, FRANCO, 66 90-94  
NUGENT, C A , 78 682-691  
NUKADA, SUSM, 74 478  
NUNGSTER, W J , 62 418-427, 63 372-380, 65 477-  
480  
NUTTFR, J E , 79 339-343  
NYKA, VALENTY, 73 251-265, 75 420-431

## O

OATWAY, WILLIAM H , JR , 63 490-492, 80 108  
O'BRIEN, BRENDAN, 73 219-228, 77 952-967  
O'BRIEN, E J , 59 30-38  
O'BRIEN, WILLIAM B , 68 874-884  
OCHS, JACOB, 66 750-757  
OCHSENF, ALTON, 70 763-783  
OCHSENF, SEYMOUR, 77 496-500  
O'CONNELL, HUGH V , 78 21-37  
O'CONNOR, JOHN B , 59 402-414, 60 264-268,  
63 312-324, 68 270-272  
ODA, U , 70 465-475, 641-664  
ODFRR, CHARLES P , 80 (Supplement, July 104-  
112)  
OECHSLI, FRANK W , 74 590-596  
OESTREICHER, ROLF, 70 504-508, 71 390-405,  
72 693  
OGAWA, G , 71 465-472  
OGAWA, YASAKA, 75 99-104  
OGINSKY, EVELYN L , 74 78-83  
OHLSON, MARGARET A , 60 455-465  
OHR, IRVING, 72 653-658  
OHTA, SHIGEO, 79 329-338  
OKANO, TAKESHI, 68 535-540  
OKAWAKI, MABEL S , 77 536-538  
O'LEARY, BETTY, 64 71-76  
O'LEARY, DENIS J , 73 501-518  
OLINGER, JOHN K , 65 88-92  
OLIVEIRA-LIMA, A , 78 346-352  
OLIVER, ROBERT K , 71 291-294  
OLSEN, ARTHUR M , 60 32-38, 74 454-456  
OLSON, BYRON J , 62 403-407, 65 48-63  
OLSON, DONALD E , 66 449-456, 68 657-677,  
70 102-108  
OLSON, EDWARD C , 75 584-587  
OLSON, HOWARD D , 75 675-677  
O'NEILL, E F , 72 577-600  
ORESKEs, IRWIN, 67 299-321, 70 334-343  
ORGANICK, AVRUM, 72 851-855, 79 799-804  
ORINIUS, ERIK, 78 368-375, 376-390, 79 450-456  
ORITT, JACOB E , 69 1045-1050  
ORMOND, LOUISE, 69 319-333, 70 228-265, 743-747  
ORNSTEIN, GEORGE G , 67 212-216

- O'ROURKE, PAUL V , 59 30-38  
 ORTON, S P , 80 388-397  
 OSATO, SHUNGO, 74 258-276  
 OSHIMA, SHUNSAKU, 76 90-109, 77 524-528, 529-535, 78 884-898  
 OSTROM, C A , 79 541  
 OSWALD, NEVILLE, 75 340-342  
 OTT, ROY H , JR , 65 692-708  
 OTTOSEN, POUL, 62 434-438  
 OUSLEY, JOSEPH L , 68 523-534  
 OVERHOLT, RICHARD H , 60 406-418, 62 491-500, 75 865-884  
 OWEN, CORA RUST, 61 705-718, 66 58-62  
 OWEN, GEORGE C , 61 474-482, 66 261-270, 67 267  
 OWENS, RUTH P , 76 899-901  
 OYAMA, TSUTOMU, 72 613-632, 73 472-484  
 OZOLS, J , 75 1007-1008, 76 159-160
- P**
- PACHTER, MAURICE, 68 796-798  
 PACKALÉN, THOROLF, 69 205-211, 80 19-25, 410-414  
 PACKARD, EDWARD N , 62 (Supplement, July 1-2), 69 50-57  
 PACKARD, JOHN S , 63 706-709  
 PADIATELLIS, C , 72 527-536  
 PAGEL, WALTER, 59 311-316, 65 673-691  
 PAHNELAS, ELIZABETH V , 73 956-959  
 PAINE, A L , 63 644-656, 78 411-425  
 PALACIOS, HECTOR, 68 760-770  
 PALCHANIS, WM T , 65 451-454  
 PALDINO, RITA L , 80 398-403  
 PALEN, M IMOGENE, 75 148-152  
 PALEY, SAMUEL S , 79 307-314  
 PALITZ, LEO S , 75 461-468, 77 232-244  
 PALMER, CARROLL E , 68 462-466, 68 678-694, 69 383-395, 73 1-18, 74 917-939, 76 517-539, 77 546-550, 877-907, 80 747-749  
 PALMER, EDDY D , 61 116-130  
 PAMPLONA, P A , 60 501-513  
 P'AN, S Y , 63 1-3, 44-48, 66 100-103  
 PANDE, A , 70 328-333  
 PANGBORN, MARY C , 66 335-344, 69 300-303  
 PANISSET, MAURICE, 71 319-321  
 PANST, FELIX, 60 121-130, 65 761-764, 67 354-365, 366-375, 68 284-285  
 PANTAZIS, S , 72 859-862  
 PAOLETTI, R , 80 110-111  
 PAPPAGIANIS, DEMOSTHENES, 74 147-148  
 PAPPENHEIMER, A M , 71 88-96, 97-111  
 PAREJA CORONEL, ARMANDO, 75 987-991  
 PARKER, F , JR , 70 130-138  
 PARKER, JUNE, 62 58-66  
 PARKER, MALCOLM V , 72 119-122  
 PARKER, ROBERT F , 76 899-901  
 PARLETT, ROBERT C , 73 637-649, 77 450-461, 462-472, 80 153-166, 886-894  
 PARROTT, D K , 74 810  
 PARSONS, ROBERT J , 66 542-547  
 PATERSON, A B , 69 806-817  
 PATIALA, JORMA, 70 453-464  
 PATNODE, ROBERT A , 60 628-633, 62 484-490, 66 99, 69 599-603, 710-723, 72 117-118, 340-344, 685-686, 856-858, 73 246-250, 75 83-92, 630-637, 78 138-139, 79 323-328, 382-383  
 PATTERSON, R A , 74 284-288  
 PATTON, ELIZABETH A , 65 1-23  
 PATTON, WILLIAM E , 67 755-778, 779-797  
 PAUL, W , 74 511-532  
 PAULEEN, M M , 70 483-489, 76 232-246  
 PAULSON, DONALD L , 64 477-488, 76 970-982  
 PAYLATOU, M , 72 859-862  
 PAWLOWSKI, JOSEPH M , 76 988-1001  
 PAYNE, HOWARD M , 60 332-342, 66 548-566, 68 103-118, 70 701-703  
 PAYSEUR, COYT R , 78 906-915  
 PEABODY, J WINTHROP, 68 775-781, 74 106-111  
 PEARSON, RAYMOND, 62 29-44  
 PEARSON, ROY T , 66 509-521, 68 177-187  
 PEASLEY, E D , 76 669-670  
 PECK, MORDANT E , 65 339-343  
 PECK, W M , 61 387-398  
 PECORA, DAVID V , 65 83-87, 73 586-588, 75 781-792, 77 83-92, 79 41-46, 134-141, 679  
 PEEPLES, WILLIAM J , 69 111-115  
 PEER, EDGAR T , 75 153-155  
 PEIZER, LENORE R , 67 598-603, 68 290-291, 734-738, 69 26-36, 1022-1028, 70 349-359, 363-366, 728-733, 71 305-307, 841-859, 72 143-150, 246-251, 74 293-296, 428-437, 76 732-751, 78 788-792  
 PEKICH, A M , 63 44-48  
 PENIDO, R F , 70 109-120  
 PENNER, MILDRED A , 63 4-6, 7-16  
 PENSO, ANGEL DE LEON, 68 760-770  
 PEPSY, J , 71 49-73, 80 167-180  
 PÉREZ-TAMAYO, RUY, 77 473-481, 79 246-250, 80 554-558  
 PERKINS, EVAN K , 66 77-85  
 PERKINS, JAMES E , 66 615-618, 77 155-161, 78 810, 80 (Supplement, October 138-139)  
 PERKINS, REX B , 75 145-147, 76 906-908  
 PERKINS, ROBERT B , 64 659-668  
 PERMUTT, SOLBERT, 77 245-259  
 PERR, HERBERT M , 63 597-602  
 PERRY, C R , 72 840-842  
 PERRY, THOMAS L , 65 325-331  
 PETERSDORF, ROBERT G , 79 238-243  
 PETERSON, AGNES, 78 871-883  
 PETTER, JOHN B , 72 453-464  
 PETTY, T , 80 (Supplement, July 147-151)  
 PFEIFER-SCHEFF, IRENE M , 62 374-389  
 PFEIFFER, EHRENFRIED E , 76 867-870  
 PFUETZE, KARI H , 63 427-433, 68 912-925, 71 752-754, 78 649-650  
 PHILLIPS, CHARLES, 79 362-370

- PHILLIPS, SAMUEL, 60 648-653, 62 549-554, 63 116-118, 69 443-450, 70 476-482, 72 667-674, 843-845, 73 704-715, 75 667-669, 78 135-137, 79 273-283, 80 641-647, 724-731, 909-910
- PHILPOT, F J, 66 28-35
- PIAGGIO, ARISTEO A, 66 1-15
- PICARD, D, 77 839-847
- PICCAGLI, RUTH W, 60 557-563
- PICKETT, WILLIAM H, 62 439-440
- PIERCE, CYNTHIA H, 74 655-666, 667-682, 683-698, 699-717, 75 331-337, 359-409, 692-693
- PIERCE, JOHN A, 80 (Supplement, July 45-48)
- PIERSON, BARBARA J, 68 48-64
- PIERSON, CHARLES E, 73 123-127
- PIETRASZEK, CASIMIR F, 70 672-688
- PIETROWSKI, JOSEPH J, 70 423-429
- PIKULA, DARIA, 67 808-827
- PILCHER, HELEN, 62 58-66
- PILLSBURY, DONALD M, 63 441-448
- PILPEL, MICHAEL, 68 782-785
- PINES, A, 79 818
- PINNER, MAX, 59 449-460
- PINNEY, CHARLES T, 74 441-444, 77 32-38
- PITAL, ABE, 78 111-116
- PITAL, RUTH C, 78 111-116
- PITNER, GEORGIA, 63 679-693
- PITTS, FORREST W, 61 862-867, 62 610-617
- PIZZALATO, PHILIP, 80 (Supplement, July 104-112)
- PLACE, RONALD, 60 706-714
- PLATOU, R V, 74 (Supplement, August 160-168)
- PLATT, WARREN D, 6 514-519
- PLESSINGER, VIRGIL A, 60 589-603
- PLUNKETT, ROBERT E, 61 51-56
- POET, RAYMOND B, 65 484-485
- POINDEXTER, HILDRUS A, 67 665-668
- POLACHEK, ABRAHAM, A, 61 868-874
- POLACK, ROBERT T, 64 307-312
- POLAYES, SILIK H, 75 326-330
- POLLAK, ANN, 71 74-87, 73 917-929
- POLLAK, MAXIM, 72 107-116
- PONGOR, FERENC, 79 652-658
- POOLE, GRAHAM, 73 805-817
- POPE, HILDA (*see also* WILLETT, HILDA POPE), 62 34-47, 68 928-939, 69 705-709, 73 735-747
- POPPE DE FIGUEIREDO, FLAVIO, 71 186-192
- POPPER, HANS, 75 295-302, 77 120-133, 80 71-77
- PORTELANCE, VINCENT, 79 296-306
- POTTENGER, F M, 60 639-647, 68 933-937
- POTTER, EDITH L, 80 (Supplement, July 5-20)
- POTTS, WILLIAM L, 64 394-407
- POWELL, MARY E, 63 717
- PRATT, PHILIP C, 59 664-673, 674-678, 62 455-474, 64 87-101, 66 194-212, 67 29-44, 69 766-789, 841-842, 70 714-727, 74 874-884, 75 93-98, 76 880-887, 77 62-72, 78 839-847
- PREHEIM, DELBERT V, 65 339-343
- PREMINGER, MAX, 66 86-89
- PREUSS, FRED, 70 285-295, 76 123-131
- PRIBEK, ROBERT A, 77 729-736
- PRICE, ZANE, 76 964-969
- PRIETO, L C, 75 259-265
- PRINCI, FRANK, 60 706-714
- PRIOR, JOHN A, 63 538-546, 66 588-593
- PRITCHARD, ELIZABETH, 75 1003-1006
- PROUDFIT, WILLIAM L, 75 469-475
- PROUT, CURTIS T, 65 481-483
- PRYOR, W W, 74 309-316
- PUBLIC HEALTH SERVICE *See* U S PUBLIC HEALTH SERVICE
- PUCKETT, THOMAS F, 67 453-476, 70 320-327
- PUFFER, RUTH R, 65 111-127
- PUZIK, V I, 79 497-501
- PYLE, MARJORIE M, 81 752-754, 78 649-650
- Q**
- QUARLES, CONSTANCE, 70 701-713
- QUINLAN, J J, 61 355-368, 79 468-473
- R**
- RACK, FRANK J, 63 227-229
- RADNER, DAVID B, 65 93-99
- RAFFEL, SIDNEY, 74 (Supplement, August 60-74), 80 849-854
- RAHN, HERMANN, 76 1063-1070
- RAINE, FORRESTER, 61 474-482
- RAKE, GEOFFREY, 60 90-108, 109-120, 121-130, 140-142, 63 556-567
- RAKOWER, JOSEPH, 67 85-93
- RALEIGH, JAMES W, 69 963-967, 73 123-127, 266-275, 75 538-552, 76 540-558
- RAMSAY, J H ROLLAND, 79 818
- RAMSEY, HAL H, 80 267-268
- RANDALL, HARRISON M, 63 372-380, 65 477-480, 69 505-510, 73 529-538, 75 843-845
- RANKIN, JOHN, 74 29-41
- RANNEY, ALBERT F, 77 908-922
- RANTZ, LOWELL A, 64 318-321
- RAPPAPORT, ISRAEL, 62 (Supplement, July 80-89)
- RASMUSSEN, HOWARD K, 72 569-576, 75 745-755
- RAUCHWERGER, SOLOMON M, 59 128-139
- RAUF, ROBERT A, 80 806-824
- RAY, C JACK, 70 763-783
- RAY, EDWARD S, 65 627-630
- RAY, HOMER, 74 830-834
- RAYL, JOHN E, 73 191-218
- READ, JOHN, 78 353-367
- REAM, CHARLES R, 72 381-385
- REAMES, H R, 75 588-593
- REBUCK, JOHN W, 69 216-226
- REDEMANN, C T, 62 475-480
- REDING, FRANKLIN S, 73 690-703
- REDLICH-MOSHIN, JEAN, 70 344-348
- REDMOND, W B, 73 907-916, 80 232-239
- REDNER, WALLACE J, JR, 67 859-868



- REEMTSMA, KEITH, 74 351-357  
 REES, R J W, 76 915-916  
 REES, ROBERTS M, 69 543-553  
 REEVES, FREDRIC C, 63 449-458  
 REEVES, J T, 80 (Supplement, July 128)  
 REGAN, FREDERIC D, 64 564-571  
 REGLI, J, 79 351-356  
 REGNA, P P, 60 808-810, 63 1-3  
 REHR, CAROLINE, 77 462-472  
 REHR, CAROLYN A, 80 886-894  
 REIDT, WILLIAM U, 76 33-46  
 REILLY, J C, 63 44-48, 66 100-103  
 REIMANN, ARTHUR F, 74 121-127  
 REINMUTH, OSCAR M, 64 508-515  
 REISER, HOWARD G, 61 323-334  
 REISNER, DAVID, 66 666-679, 71 841-859  
 REISS, JACK, 76 315-319  
 RENZETTI, ATTILIO D, JR, 64 583-601, 74 128-135, 75 638-643, 78 101-202, 79 72-77  
 REPA, J J, 63 587-590  
 RESNICK, ALBERT, 62 128-143  
 REUBER, MELVIN D, 72 675-684  
 REYNOLDS, LESTER T, 60 773-787  
 REHNS, MELVIN S, 72 210-217, 73 563-570, 571-575, 74 229-238, 239-244, 756-763, 764-772, 75 958-964, 78 259-267, 79 622-630, 631-640  
 RHULAND, L E, 75 588-593, 77 976-982  
 RICHARDSON JONES, A, 68 739-745  
 RICHARDSON, RUSSELL, 65 (Supplement, January 1-50)  
 RICHBURG, PAUL L, 71 693-703, 76 47-63  
 RICHERT, JOEL H, 80 760  
 RICHMOND, LEA, 62 632-637  
 RIDDELL, R W, 70 442-452, 80 167-180  
 RIEBER, CHARLES W, 63 213-219, 64 448-452  
 RIEMENSNIER, DICK K, 75 675-677, 992-994, 995-998, 76 152-158, 683-691, 80 108-110  
 RIGDON, R H, 61 247-256  
 RIGGINS, H McLEOD, 59 140-147, 62 572-581, 67 74-84  
 RIGGS, HELENA E, 74 830-834  
 RIGLER, LEO, 69 566-584  
 RIKLI, ARTHUR E, 79 427-439  
 RILEY, EDGAR ALSOP, 62 231-285, 67 613-628, 71 584-591, 80 426-430  
 RILEY, RICHARD L, 71 249-259, 75 420-431, 76 931-941  
 RIST, NOEL, 74 (Supplement, August 75-89), 79 1-5, 6-18  
 RITTENBERG, DAVID, 71 609-616  
 RITTER, NATHANIEL S, 62 586-593  
 RIVOIRE, ZINA C, 67 808-827  
 ROBB, C J, 80 110  
 ROBBINS, S L, 70 130-138  
 ROBERTS, ALBERT, 80 582-584  
 ROBERTS, E GWYN, 60 634-638, 61 563-568  
 ROBERTS, GYWN, 64 557-563  
 ROBERTS, ROBERT W, 80 904-908  
 ROBERTSON, DOUGLAS H, 69 618-624  
 ROBINS, ARTHUR B, 69 26-36, 1057-1058, 70 1042-1053, 72 143-150, 74 293-296, 480, 75 41-52, 77 359-363, 78 725-734  
 ROBINSON, ARTHUR, 71 765-766  
 ROBINSON, FRANCES, 69 1016-1021, 1051-1053, 76 703-705  
 ROBINSON, G CANBY, 63 365-371  
 ROBINSON, HARRY J, 68 212-219, 70 423-429, 74 972-976  
 ROBINSON, JERRYDEAN H, 62 484-490  
 ROBINSON, JOE S, 77 73-82  
 ROBINSON, JOSEPH L, 73 690-703  
 ROBITZEK, EDWARD H, 65 402-428, 67 212-216  
 ROBSON, J M, 74 1-6, 75 756-767, 78 203-225, 80 871-875  
 ROCHE, A D, 77 839-847  
 ROCHE, PAT, JR, 65 603-611  
 ROCKELY, E E, 78 815-821, 79 773-779  
 RODRÍGUEZ PASTOR, J, 67 132-153, 70 1099-1101  
 ROE, M D, 65 376-391  
 ROESSLER, WILLIAM G, 73 716-725  
 ROGERS, A E T, 61 643-647, 70 285-295  
 ROGERS, BETTY S, 76 568-578  
 ROGERS, DAVID E, 69 1029-1036, 71 371-381  
 ROGERS, WILLIAM K, 74 188-195  
 ROGERS, WILLIAM L, 71 30-48, 77 418-422  
 ROGUL, MARVIN, 76 697-702  
 ROLL, LEWIS R, 69 84-91  
 ROMÁN, ELVIRA, 77 146-154  
 ROMANSKY, MONROE J, 80 590-593  
 ROORBACH, ELIZABETH H, 72 465-478  
 ROPER, WILLIAM H, 61 678-689, 725-729, 71 616-634, 72 242-244, 75 1-40  
 RORABAUGH, MILDRED E, 67 432-439  
 ROSCH, PAUL J, 70 841-851  
 ROSE, HAROLD D, 80 249-254  
 ROSE, ISADORE, 65 332-338  
 ROSE, N R, 78 637-643  
 ROSENBLATT, GEORGE, 76 909-911  
 ROSENTHAL, IRA M, 62 441-445  
 ROSENTHAL, SOL ROY, 60 236-248, 61 95-105, 106-115, 730-734, 64 698-701, 65 344-346, 641, 77 778-788, 79 105  
 ROSENZWEIG, ABRAHAM L, 70 176-177  
 ROSNER, BEN, 70 285-295  
 ROSS, JOSEPH, 62 109-111, 63 67-75  
 ROSS, S GRAHAM, 76 832-851  
 ROTH, LLOYD J, 75 71-82  
 ROTHSTEIN, EMIL, 59 39-49, 50-52, 64 686-690, 66 233-239, 381, 69 65-70, 287-296, 980-990, 70 509-517  
 ROUCH, L C, 78 251-258  
 ROULET, F, 68 771-774  
 ROUTIEN, J B, 63 1-3  
 ROWE, CHARLOTTE, 63 667-671, 66 621-622  
 ROYE, W E, 70 373-377

RABLO, SYDNEY D., 68 331-345, 346-359, 78 251-258, 79 392-396  
 RABPMAN, WILLIAM, 76 761-769  
 RUBIN, BERNARD, 65 332-401, 67 641-651  
 RUTIN, MORRIS, 69 273-287  
 RYAN, RUTH C., 80 555-565  
 RYAN, DAVID, 76 130-137  
 RYAN, LYNN H., 70 374, 79 663-665, 80 277-278  
 RYAN, CHARLES, 74 550-551  
 RYAN, HENRY P., 72 275-281, 719-717  
 RYAN, KRISTIN P., 63 403-697  
 RYAN, M., 62 485-514  
 RYAN, MORRIS, 68 765-768  
 RYAN, WILLIAM F., JR., 65 619-620, 70 1030-1041, 71 3 9-103 141-146, 73 944-955, 74 (Supplement, August 267-277), 79 797, 79 665-668, 80 567-568  
 RYAN, THOMAS C., 61 42-470  
 RYAN, EDWARD T., 77 1026-1029

## S

SADLER, JOSEPH I., JR., 59 402-414  
 SAGAWA, I., 71 465-472  
 SAGE, WILLIAM H., III, 72 663-676, 74 622-623  
 SAHA, STANLEY H., 62 219-222  
 SAHA, JOSEPH J., 65 791-802  
 SAIFER, ABRAHAM, 67 299-321, 70 334-343, 71 15-28  
 ST. PIERRE, JACQUES, 79 299-306  
 ST. RAYMOND, ALBERT H., JR., 71 295-298  
 SAKAGUCHI, SAKI, 62 615-653  
 SALANT, MYRON, 64 448-452  
 SALKIN, DAVID, 63 721-722, 71 761-370, 74 376-387, 77 181-183, 80 50-61, 117-119  
 SALOMON, A., 69 915-929  
 SALOMO, ALEXANDER, 74 121-127  
 SALZMAN, EMMETT, 68 788-790  
 SAMADI, A., 71 319-760  
 SAMMON, PAUL C., 73 451-471, 77 561-592  
 SAMUEL, K. C., 76 410-425  
 SANDAGE, CURTIS, 61 556-559  
 SANDERSON, STEPHENS S., 68 157-164  
 SANDHAUS, HAROLD S., 64 170-181  
 SANDLER, BENJAMIN P., 76 370-387  
 SANDPOCK, MARION S., 65 210-214  
 SANDROCK, RACHIEL S., 65 210-214  
 SANDS, JAMES H., 66 531-541, 69 58-61  
 SANFORD, JAY P., 73 581-585  
 SANGER, GRANT, 69 618-624  
 SARRER, R. W., 59 692-700, 62 418-427, 66 351-356  
 SARIN, L. R., 76 410-425  
 SARTWELL, PHILIP E., 59 481-493, 63 608-612  
 SASANO, K. T., 59 461-465  
 SASLAV, SAMUEL, 66 588-593  
 SAVAGE, G. M., 75 576-583  
 SAXHOLM, ROLF, 69 304-306, 72 98-106, 74 616-621  
 SBAR, SIDNEY, 65 589-595

SBARRA, ANTHONY J., 77 669-671, 675-680, 79 810-812  
 SCARBOROUGH, C. GIRAUD, 60 631-638  
 SCHAEDLER, RUSSELL W., 73 781-784, 75 331-337, 359-409  
 SCHAFFER, GEORGE, 70 49-60, 1096-1098, 72 810-821, 75 501-505, 78 697-711  
 SCHAFFER, J. ALBERT, 75 638-643  
 SCHAFFER, WERNER B., 65 75-82, 68 273-276, 69 125-127, 70 552-572, 71 683-698, 75 656-658  
 SCHAFF, BURNETT, 61 353-351, 71 129-136, 71 138-140  
 SCHAFFID, HENRY G., 69 520-512  
 SCHALLER, WILLIAM, 69 261-266  
 SCHLICHTER, M. MURRAY, 68 603-614  
 SCHRIER, GEORGE J., 62 371-389  
 SCHREIBER, G. W. H., 78 512-523  
 SCHIRACIO, M., 75 807-822, 77 815-822  
 SCHICK, BEILA, 71 (Supplement, August 290-296)  
 SCHILFNER, IRANK S., 75 667-669, 1003-1006  
 SCHIRRES, JAMES M., 76 811-831, 80 569-574  
 SCHMIDT, CHARLES E., 71 152-156  
 SCHMIDT, HANS, 61 1-7  
 SCHMIDT, HARMAN W., 78 773-778, 779-784  
 SCHMIDT, HERBERT W., 73 52-60  
 SCHMIDT, L. H., 67 798-807, 70 266-273, 74 (Supplement, August 138-152), 75 169-179  
 SCHMIDT, PETER P., 66 591-600  
 SCHNIDAU, JOHN D., JR., 76 770-788  
 SCHNIDDER, LEO V., 73 966  
 SCHNEIDER, RFA M., 76 579-587  
 SCHNITZER, ROBERT J., 65 759-760, 67 674-675, 68 277-279  
 SCHOMER, A., 59 632-635  
 SCHUCK, MILFORD H., 68 9-23  
 SCHULMAN, IRVING, 62 618-631  
 SCHULTZ, RICHARD L., 77 536-538  
 SCHURR, ALIAN, 65 511-518  
 SCHWARTZ, ARTHUR, 74 533-540  
 SCHWARTZ, BENJAMIN, 66 591-600  
 SCHWARTZ, EMANUEL, 71 811  
 SCHWARTZ, MORTON, 70 731-738  
 SCHWARTZ, PHILIP, 67 110-152  
 SCHWARTZ, S., 69 1057-1058  
 SCHWARTZ, SPYMOUR I., 76 1063-1070  
 SCHWARTZ, STEVEN O., 60 660-669  
 SCHWARTZ, WILLIAM S., 61 875-880, 64 41-49, 66 436-448, 70 413-422, 924, 76 1097-1099, 79 90-93  
 SCHWARZ, CH., 74 475-476, 77 999-1004, 70 97-101  
 SCHWARZ, JAN, 76 173-194, 77 162-167  
 SCHWELGER, OTTO, 77 146-154, 78 735-748  
 SCOTT, H. WILLIAM, JR., 65 48-63  
 SCOTT, NANCY B., 62 121-127  
 SCOTT, PAUL W., 77 329-337  
 SCOTT, ROBERT A., 77 990-998  
 SCOTT, STEWART M., 76 1002-1006  
 SEABURY, JOHN H., 77 511-515

- SEAGLE, JOSEPH B , 67 341-353  
 SEAMAN, JAMES B , 79 681  
 SEGAL, MAURICE S , 69 915-929, 74 210-220,  
 77 1-9,80 38-45,46-52,53-58  
 SEGAL, WILLIAM, 71 112-125,228-248, 75 495-500  
 SEIBERT, FLORENCE B , 59 86-101,585-594, 62 67-  
 76,77-86, 65 201-205, 66 314-334, 71 704-721,  
 73 547-562, 75 601-607  
 SEIBERT, MABEL V , 62 67-76, 73 547-562  
 SEIFE, MARVIN, 63 202-209  
 SEILER, HAWLEY H , 63 81-84  
 SEINFELD, EDWARD, 80 845-848  
 SELIKOFF, IRVING J , 65 402-428, 67 212-216  
 SELIN, MERLE J , 78 944-948, 79 663-665  
 SELKON, J B , 74 (Supplement, August 109-116)  
 SELL, H M , 62 475-480  
 SELLERS, MARGRET IRENE, 76 964-969  
 SELYE, HANS, 67 677-678, 71 319-321  
 SENDERI, MARY, 76 108-122  
 SEN-GUPTA, N C , 66 151-160  
 SEPP, ENDEL, 76 167-172  
 SETTLE, JANET, 70 734-738  
 SEVER, JOHN L , 75 280-294, 76 616-635  
 SEVRINGHAUS, ELMER L , 62 360-373, 68 165-  
 176,470  
 SEWELL, EDWARD, 66 623-625  
 SEYBOLD, WILLIAM D , 61 193-200  
 SHABART, E J , 76 892-895  
 SHAFER, MORRIS F , 76 770-788  
 SHAMASKIN, ARNOLD, 62 563-571  
 SHANE, S J , 62 331-332  
 SHAPIRO, ROBERT, 69 1042-1044  
 SHARMAN, I M , 80 223-231  
 SHAUFFER, IRVING, 76 761-769  
 SHAW, CHARLES R , 62 58-66  
 SHAW, J BRIAN, 69 724-733  
 SHAW, K M , 70 274-284  
 SHAW, LAWRENCE W , 68 462-466, 77 877-907  
 SHAW, ROBERT R , 76 970-982  
 SHEEHY, JOHN J , 61 77-94  
 SHEEHY, THOMAS F , JR , 74 835-855  
 SHEETS, LAWRENCE M , 61 369-386, 68 505-522  
 SHELDON, WALTER H , 65 596-602  
 SHELTON, NEIL W , 79 273-283  
 SHEPARD, C C , 77 423-435, 968-975  
 SHEPARD, RICHARD H , 71 249-259  
 SHEPARDSON, H CLARE, 67 544  
 SHER, BEN C , 75 295-302, 77 120-133  
 SHERAGO, M , 76 888-891  
 SHIELDS, D O , 75 53-61, 76 47-63  
 SHIELDS, T W , 78 822-831  
 SHIPMAN, SIDNEY J , 60 788-793, 64 225-248,  
 67 544  
 SHIVPURI, D N , 76 799-810  
 SHOPE, ROBERT E , 79 238-243  
 SHORT, E I , 80 167-180  
 SHULRUFF, ELI, 74 121-127  
 SHULTZ, HENRY H , 77 923-930  
 SHUMAN, CHARLES R , 64 630-644  
 SIBLEY, JOHN C , 62 314-323  
 SIDES, LeROY J , 63 275-294  
 SIEBENMANN, CHARLES O , 68 411-418  
 SIEBENS, ARTHUR A , 69 869-914, 70 672-688,  
 71 676-692, 80 806-824  
 SIEGEL, HENRY, 60 366-376, 70 423-429, 74 972-976  
 SIEKER, H O , 74 309-316  
 SIEMSEN, JAN K , 75 303-318  
 SIFONTES, JOSE E , 67 732-754, 74 (Supplement,  
 August 225-231), 76 388-397  
 SILEN, W , 80 (Supplement, July 147-151,155-156)  
 SILVERMAN, CHARLOTTE, 60 466-482  
 SILVERMAN, GERTRUDE, 61 525-542  
 SILVERMAN, IRVING, 60 354-358, 61 442  
 SILVERMAN, J D , 62 209-212  
 SILVERMAN, MILTON, 62 87-90  
 SILVERTHORNE, M CLARK, 61 525-542  
 SIMINOFF, PAUL, 75 576-583  
 SIMMONS, DANIEL H , 76 195-214  
 SIMMONS, GEORGE, 62 128-143  
 SIMON, THOMAS R , 62 594-609  
 SIMPLER, AGNES THRESE (SISTER), 76 506-507  
 SIMPSON, DAVID G , 80 426-430  
 SIMPSON, ROBERT M , 60 343-353  
 SINGER, ELLIS P , 76 132-139  
 SINGER, JACQUES, 65 779-782  
 SINGLETON, ALBERT O , JR , 62 439-440  
 SKAGGS, JOSEPH T , 72 647-652  
 SKAVLEM, JOHN H , 68 296-297, 71 163-164  
 SLAVIN, PAUL, 60 755-772, 65 142-158  
 SLOTNIK, IRVIN, 61 742-746  
 SMALL, MAURICE J , 61 893, 63 591-596, 70 191-218,  
 72 386-389, 75 242-255, 77 184-188  
 SMILEY, GEORGE W , 72 647-652  
 SMITH, CARLISLE C , 78 682-691  
 SMITH, C EDWIN, 65 617-626, 67 878-880, 75 199-  
 222  
 SMITH, CHARLES E , 72 64-70, 74 245-248  
 SMITH, C RICHARD, 59 589-598, 63 470-475,  
 70 916-919, 75 618-623, 624-629, 76 752-760,  
 80 216-222  
 SMITH, DAVID T , 62 121-127, (Supplement, July  
 34-47), 64 508-515, 67 201-211,707-721, 70 547-  
 556,557-569,570-576  
 SMITH, DONALD W , 63 372-380, 65 477-480, 69 505-  
 510, 73 529-538, 75 843-845, 77 662-668, 79 94-  
 96, 80 876-885  
 SMITH, GEORGE B , JR , 70 547-556,557-569  
 SMITH, GRAFTON A , 69 869-914  
 SMITH, I MACLEAN, 75 359-409  
 SMITH, MAPHEUS, 60 773-787  
 SMITH, M I , 59 438-448, 60 62-67, 63 100-107,  
 68 119-126  
 SMITH, MARJORIE M , 66 194-212, 71 308-313,  
 73 768-772, 75 180-198, 76 497-502,643-659,  
 78 454-461,570-575

- SMITH, N, 66 125-133, 67 322-340, 69 479-494,  
72 53-63
- SMITH, ROBERT M, 63 1-6, 7-16, 75 576-583
- SMITH, RODNEY P, 69 551-565
- SAFLI, W E, 70 755
- SAIDFR, GORDON, 61 50-63, 65 93-99
- SAJJID R, J, 78 547-562
- SADIN, B A, 63 1-3
- SOCHOCKA, S, 78 103-110, 916-920, 79 502-511
- SÖDERHOLM, B, 75 721-729
- SOKOLOFF, MARTIN J, 69 161-172, 73 239-245
- SOKOLSKI, WALTER T, 75 576-583
- SOLOMON, H J, 77 192-195
- SOLOTOROVSKI, MORRIS, 60 366-376, 65 718-721,  
68 212-219, 70 806-811, 71 59-67, 68-71, 72-  
77, 78-83
- SOLTIS, M A, 61 399-405
- SOMMER, GEORGE N J, JR, 67 232-246, 68 782-785
- SOMMERWEYER, LUCILLE, 67 530-534, 68 419-424
- SONLS, MAURICE, 62 408-417, 67 671-673
- SOOS, I, 77 146-151
- SORKIN, E, 67 629-643
- SOTO FIGUEROA, EVA, 71 704-721, 73 547-562,  
75 601-607, 78 93-100
- SPAIN, DAVID M, 62 114-118, 337-344, 63 339-345,  
65 692-705, 66 621-622, 67 101-102, 68 24-30,  
76 559-567, 79 591-596
- SPARR, HAROLD A, 61 826-831
- SPEARS, R G, 64 516-519
- SPENCE, MARTHA JANE, 69 111-115
- SPEACER, GEORGE E, 62 209-212, 75 833-835
- SPENDLOV, GEORGE A, 60 628-633
- SPENGOS, THEODORE N, 77 858-862
- SPEYER, JOSEPH F, 75 517-518, 77 501-505
- SPIES, HAROLD W, 69 192-204
- SPINO, PASCAL D, 62 209-212
- SPITZ, LEON J, 66 594-600
- SPIVEY, C G, 80 259-261
- SPORER, ANDREW, 61 508-517
- SPRICK, MARIAN G, 74 552-565
- SPOULL, BRIAN J, 79 315-322
- STÄHLE, INGVAR, 66 271-284, 285-291, 78 368-  
375, 376-390, 79 450-456
- STÄLLBERG-STENHAGEN, S, 75 699-709
- STANDER, HERBERT, 65 761-764, 68 284-285
- STANONIS, DAVID J, 76 852-861
- STARR, PAUL, 80 845-848
- STASKIEL, L J, 79 512-517
- STASKO, IRENE, 78 934-938, 939-943, 80 274-276
- STAUDT, LOUIS W, 61 705-718
- STAUSS, HANS-KARL, 71 473-502, 73 165-190
- STEAD, WILLIAM W, 71 473-502, 529-543, 74 897-  
902
- STEELE, JAMES H, 77 908-922
- STEELE, JOHN D, 60 383, 62 645-653, 63 76-80,  
64 117-118, 66 261-270, 67 267, 69 636-637,  
71 144-145, 73 960-963, 76 902-905, 77 368
- STEENKEN, W, JR, 59 221, 429-437, 664-673, 664-  
668, 62 101-108, (Supplement, July 22-  
33), 300-306, 63 30-35, 64 87-101, 65 365-  
375, 751-758, 66 194-212, 68 65-74, 548-556,  
70 367-369, 370-372, 375, 714-727, 71 308-313,  
73 72-78, 123-127, 539-546, 768-772, 75 180-198,  
316-347, 510-513, 965-974, 76 497-502, 643-659,  
78 151-461, 570-575, 79 66-71
- STEFFEN, CHARLES G, 69 116-120
- STEFFKO, P L, 65 376-391
- STEIN, HANS F, 61 645-658, 67 477-489
- STEIN, HAROLD L, 74 99-105
- STLIN, SAMUEL C, 62 403-417, 66 188-193, 68 695-  
712, 73 239-245
- STEINBACH, M M, 59 624-631, 61 868-874
- STEINBERG, BERNARD A, 65 357-364, 67 354-365,  
366-375
- STEINBERG, ISRAEL, 62 353-359
- STEININGER, WILBUR J, 67 286-291, 292-298,  
69 451-454, 70 518-520, 533-534, 71 766
- STEMMERMAN, GRANT N, 62 324-330
- STEPANIAN, E S, 79 142-151
- STEPHANOPOULOS, CONSTANTIN, 76 1079-1087
- STEPHENS, H BRODIE, 60 788-793
- STEPHENS, MARGARET G, 60 487-500, 70 601-609
- STERGUS, INGRID, 75 199-222, 223-241
- STERLING, KENNETH, 62 112-115
- STERN, K F, 75 588-593, 77 976-982
- STERN, KURT, 64 696-697
- STERNLIEB, RICHARD O, 77 729-736, 80 249-254
- STEVEN, I, 78 932-933
- STEVENS, ROBERT P, 66 722-731
- STEVLICK, CHARLES P, 78 135-137
- STEWART, DOROTHY M, 66 36-43
- STEWART, DONALD B, 69 745-758
- STEWART, SHEILA M, 69 641, 73 390-405, 406-421
- STIEF, MARION, 74 478-480
- STIMPFT, F D, 62 418-427
- STINEBRING, WARREN R, 78 712-724
- STINSON, FRANCES LOUISE, 76 896
- STOCKLEN, JOSEPH B, 79 427-439
- STOKES, A M, 62 572-581, 66 16-27
- STOKINGER, HERBERT E, 60 359-363
- STONE, DANIEL J, 74 533-540
- STONE, MILDRED, 72 633-646
- STONE, WILLIAM F, JR, 61 422-425
- STOREY, CLIFFORD F, 64 327-352, 69 869-914,  
70 672-688, 71 635-667, 676-692, 72 257-267
- STOREY, PATRICK B, 68 760-770, 70 881-891,  
73 117-122, 75 514-516
- STOW, ROBERT M, 61 705-718
- STRAEHLEY, CLIFFORD J, JR, 75 638-643
- STRAIN, ANNE K, 79 47-51
- STRANG, VERDA G, 76 568-578
- STRAUSS, RICHARD E, 63 441-448
- STREETER, BILLIE B, 77 32-38
- STRIEDER, JOHN W, 63 547-555, 67 3-21, 77 716-  
718
- STRINGER, C J, 60 455-465, 74 856-873

- STROM, LARS, 74 (Supplement, August 28-31)  
STROUMBOU, S, 72 859-862  
STUART, DOUGLAS G, 79 253-255  
STUDY, ROBERT S, 69 53-67  
STUTZMAN, FRANCIS L, 66 357-363  
SUHRLAND, LEIF G, 60 359-363  
SULA, L, 80 438-440  
SULLIVAN, B H, 67 859-868  
SULLIVAN, F M, 75 756-767, 78 203-225, 80 871-875  
SULLIVAN, ROBERT D, 69 957-962  
SUNKES, E J, 65 617-626, 67 878-880  
SUTER, EMANUEL, 60 384, 65 775-776, 69 1060-1062, 70 793-805, 79 47-51  
SUTHERLAND, IAN, 71 314-315, 317-318  
SUTLIFF, W D, 75 912-920  
SUYEMOTO, DOROTHY, 69 733-744  
SWALBACH, W GEORGE, 76 1063-1070  
SWARTZ, IRENE B, 61 765-797  
SWEANY, HENRY C, 60 576-588, 61 569-577  
SWEANY, JOAN, 61 569-577  
SWENSON, EDWARD W, 71 676-692, 75 699-709, 710-723, 76 983-987  
SWIFT, WILLIAM E, JR, 59 402-414  
SWINDELL, HERBERT, 68 505-522  
SYPHAX, GRACE B, 70 701-713  
SZE, KENNETH CHIACHE, 71 349-360  
SZENT-GYORGYI, NÁNDOR, 76 308-314  
SZYBALSKI, WACLAW, 65 768-770, 68 280-283, 631-633, 69 267-279
- T**
- TABAKIN, BURTON S, 80 825-832  
TABER, RODMAN E, 72 801-809  
TAGER, MORRIS, 67 538  
TAKEOKA, ATSUKO, 77 524-528, 529-535, 78 884-893  
TAKEYA, KENJI, 80 543-553  
TAKIMURA, YOSH, 75 295-302, 77 120-133  
TAMURA, MASASHI, 71 465-472  
TANI, JUNKICHI, 79 738-745  
T'AO, J C, 80 359-370  
TAPLIN, GEORGE V, 79 374-377  
TARNOWSKI, CURT E, 73 598-600, 76 159  
TARSHIS, MAURICE, 64 551-556, 65 278-288, 289-301, 302-315, 67 391-395, 72 119-122, 73 601-603, 74 84-91, 78 921-926  
TASHIRO, K, 78 637-643  
TATE, K B, 63 1-3  
TATSUOKA, MAURICE, 73 472-484  
TAYLOR, HELEN C, 70 71-90, 72 35-52, 245, 74 7-14  
TAYLOR, RICHARD R, 77 1023-1025, 79 641-651  
TAYLOR, ROBERT L, 77 1023-1025  
TAILOR, WARREN J, 72 453-464  
TCHEH, PETER A, 72 479-486, 76 144-151  
TEDESCO, JOSEPH F, 63 393-399  
TELLESSE, W G, 78 251-255
- TEMPEL, CARL W, 62 563-571, 63 295-311, 66 534-541, 69 58-64, 73 117-122, 165-190  
TERAI, TAKEO, 79 738-745  
TERPLAN, KORNEL L, 74 (Supplement, August 7-12)  
TERRILL, ARTHUR A, 68 505-522  
THALHIMER, WILLIAM, 63 667-671  
THEODOS, PETER A, 65 24-47  
THIGPEN, FRANCIS M, 71 291-294  
THOMAS, BERNARD G H, 65 392-401  
THOMAS, GORDON W, 63 76-80  
THOMAS, SIDNEY F, 66 502  
THOMPSON, BRIAN C, 75 885-896  
THOMPSON, J ROBERT, 66 161-174, 69 247-260, 72 158-170, 601-612, 77 931-939, 80 71-77  
THOMPSON, MILLIE A, 80 216-222  
THOMPSON, S A, 78 815-821, 79 773-779  
THOMPSON, T L, 74 284-288  
THOMSON, ROBERT V, 71 429-436  
THOREN, MILDRED, 74 142-144  
THURSTON, JOHN R, 71 419-428, 72 210-217, 633-646, 73 338-350, 563-570, 571-575, 74 756-763, 764-772, 75 958-964, 77 311-322, 79 66-71  
TICKNER, CLAIRE, 72 297-329  
TILLET, WILLIAM S, 76 1-21  
TIRUNARAYANAN, M O, 75 62-70, 80 559-568  
TITSWORTH, E H, 67 674-675  
TOBIN, C E, 80 (Supplement, July 50-56)  
TODA, TADAO, 80 543-553  
TOGURI, EIZO, 78 927-931  
TOKUJAMA, GEORGE, 78 871-883  
TOKUYASU, KIYOTERU, 76 964-969  
TOMASHEFSKI, JOSEPH F, 71 333-348, 72 479-486  
TOMPSETT, RALPH, 63 49-61, 64 295-306, 696-697, 69 313-333, 70 91-101, 743-747, 748-754, 72 851-855, 74 (Supplement, August 100-108), 471-473, 572-580  
TONG, JAMES L, 78 604-609  
TONGE, J I, 73 930-939  
TORMEY, DAVID M, 67 859-868  
TOWBIN, MILTON N, 63 295-311  
TOWNSEND, SAMUEL M, 76 315-319, 79 677  
TREVATHAN, ROBERT D, 80 909-910  
TRIMBLE, HAROLD GUYON, 74 476-478  
TSAI, SHIH H, 78 106-110, 899-905  
TSENG, LEN, 68 771-774  
TSIKOUDAS, EVANGELOS C, 76 588-600  
TSUJI, SHUSUKE, 72 393-397, 76 90-102, 77 524-528, 529-535, 78 884-893  
TSUKAMURA, MICHIO, 75 608-617, 76 298-300, 301-307, 77 346-349, 519-523, 78 121-126, 79 371-373  
TSUKAWARA, HYOTE, 74 258-276  
TUCHMAN, HERMAN, 70 171-175  
TUCKER, ELOH B, 79 344-350  
TUCKER, HAROLD A, 63 657-666  
TUCKER, WILLIAM B, 60 715-754, 61 159-169, 70 629-700, 812-840, 72 718-732, 733-755, 756-782, 78 333-345, 832-838

TUKEY, JOHN W , 62 77-86  
 TUNÇMAN, S , 80 410-414  
 TURNBULL, F W A , 73 406-421  
 TURNER, GEORGE C , 60 576-583  
 TURNER, HOWARD G , JR , 68 253-262  
 TURNER, MILLER, 74 464-467  
 TURNER, OTIS D , 68 103-118, 70 593-600, 701-713  
 TUTTLE, WM L , 59 30-38  
 TYLER, FRANK H , 78 682-691  
 TYSAROWSKI, WIESLAW, 80 257-258  
 TYSON, M D , 75 730-744

## U

ULRICH, ELIZABETH W , 75 667-669  
 URBANČÍK, RICHARD, 76 706-707, 78 802-805  
 U S PUBLIC HEALTH SERVICE, 66 632-635, 67 108-113, 553-567, 539-543, 68 264-269, 69 1-12, 70 521-526, 74 196-209, 76 942-963, 80 317-387, 627-640, 757-759  
 USTVEDT, HANS JACOB, 74 (Supplement, August 32-42)  
 UVAROVA, O A , 79 497-501  
 UYEDA, CHARLES T , 80 849-854  
 UYENO, SHIGEICHI, 76 279-285

## V

VAICHULIS, E M K , 80 262-263  
 VALENTINE, ELEANOR H , 78 604-609  
 VANCE, JOHN W , 76 64-75  
 VAN DER HOEVEN, LUDOLPH H , 76 144-151  
 VANDERLINDE, ROBERT J , 61 483-507, 63 96-99  
 VANDIVIERE, H MAC, 65 617-626, 66 95-98, 67 878-880, 77 802-814, 78 799-801  
 VANDRA, EDIT, 78 735-748  
 VAN LIEW, RUTH M , 76 1007-1015  
 VAN ORDEN, L S , 71 743-751  
 VAN ORDSTRAND, HOWARD S , 71 668-675  
 VARDAMAN, THOMAS H , 68 425-438, 439-443, 444-450  
 VARGAS JIMÉNEZ, FEDERICO, 74 903-916  
 VAUGHAN, GEOFFREY, 76 331-345, 346-359  
 VAUGHAN, LAURENCE H , 72 386-389  
 VELASQUEZ, TULIO, 59 364-390  
 VENKITASUBRAMANIAN, T A , 78 117-120  
 VENNESLAND, KIRSTEN, 59 554-561  
 VERHOEFF, DIRK, 79 357-361  
 VERNHES, A , 77 839-847  
 VERSTRAETEN, JEAN M , 67 779-797  
 VESTAL, BETTY L , 80 806-824  
 VETERANS ADMINISTRATION—ARMED FORCES, 72 718-732, 733-755, 756-782, 73 960-963, 74 897-902, 76 360-369  
 VETERANS ADMINISTRATION—NATIONAL TUBERCULOSIS ASSOCIATION, 72 866-868  
 VIEHMAN, ARTHUR J , 70 923  
 VIGIL TARDON, C , 75 345-346

VILLNOW, J , 74 475-476, 77 999-1004, 79 97-101  
 VINDZBERG, WILLIAM V , 68 874-884  
 VINK, H H , 74 633-637  
 VIRÁGH, ZOLTAN, 79 652-658  
 VISCHER, W A , 71 88-96, 97-111, 75 62-70, 80 559-568  
 VISWANATHAN, R , 70 328-333, 73 294-295, 296-300, 78 117-120  
 VITAGLIANO, GUY R , 72 543-547  
 VIVAS, J R , 60 1-14  
 VOGEL, HENRY, 77 823-838  
 VOGEL, R A , 70 498-503, 76 692-696  
 VOLJAVEC, B F , 80 388-397  
 VOLK, BRUNO W , 67 299-321, 70 334-343  
 VOLK, WESLEY A , 73 589-592  
 VORWALD, A J , 62 (Supplement, July 13-21), 455-474, 69 766-789, 841-842  
 VOSSENAAR, TH , 78 547-562  
 VYSNIAUSKAS, CONSTANTINE, 69 121-124, 759-762, 70 536

## W

WAALER, HANS, 74 297-303  
 WADDINGTON, A L , 78 251-258  
 WADE, H W , 68 295-296  
 WADLEY, F M , 60 131-139  
 WAGNER, RAYMOND D , 62 190-208  
 WAGNER, ROBERT R , 68 270-272  
 WAIFE, S O , 65 735-743  
 WAINGORTIN, ERNESTO, 74 277-283  
 WAKSMAN, BRYON H , 68 746-759, 69 1002-1015  
 WAKSMAN, SELMAN A , 60 78-89, 67 261-264, 70 1-8  
 WALDRON EDWARD, DEIRDRE, 74 798-801  
 WALKER, ARTHUR M , 69 854-857  
 WALKER, HASTINGS H , 68 839-862  
 WALKER, RHEY, 66 534-541  
 WALL, NORMAN M , 71 544-555  
 WALLACE, GORDON D , 78 576-582  
 WALLACE, JACK L , 61 563-568  
 WALLACE, STUART, 66 151-160  
 WALLACH, JACQUES B , 73 110-116  
 WALLGREN, ARVID J , 76 715-725  
 WALLNER, LINDEN J , 66 161-174, 69 247-260  
 WALSH, ARTHUR J , 77 952-967  
 WALSH, JOHN J , 72 663-666, 74 464-467, 622-623, 79 251-252, 531-532  
 WALTER, ALBERT, 80 911  
 WALTERS, HENRY W , 68 455-457  
 WALTON, S T , 61 875-880  
 WALZ, DONALD, 69 261-266  
 WANDELT, MABEL A , 70 490-497  
 WARD, D E , 72 659-662  
 WARDRIPI, BUFORD H , 60 634-638  
 WARE, PAUL F , 73 165-190  
 WARING, JAMES J , 61 678-689, 62 (Supplement, July 68-75), 71 616-634, 74 821-829, 75 1-40  
 WARREN, SARAH, 65 627-630

- WARREN, SOL L , 69 153-163  
 WARRING, FREDERICK C , JR , 60 149-167, 63 579-586, 65 235-249, 75 303-318, 80 445-446  
 WASHINGTON, EDWARD L , 59 289-310  
 WASSERBURGER, R H , 74 388-399  
 WASSERMAN, J , 80 19-25, 410-414  
 WASZ-HOCKERT, OLE, 74 471-473, 572-580, 76 256-262  
 WATERMAN, DAVID H , 74 188-195  
 WATSON, DENNIS W , 61 798-808, 63 718-720, 64 602-619  
 WATSON, RAYMOND R , 73 773-775  
 WATSON, T R , JR , 75 730-744  
 WAYNE, LAWRENCE G , 70 910-911, 71 361-370, 73 600-601, 74 376-387, 76 451-467, 468-479, 77 1030-1031, 79 526-530, 80 912-913  
 WEAVER, JOHN, 70 672-688  
 WEBB, CHARLES R , 76 899-901  
 WEBB, GEORGE N , 72 12-34  
 WEBB, WATTS R , 79 780-789  
 WEBSTER, B H , 73 485-500, 76 286-290  
 WECHSLER, HERMAN, 76 909-911  
 WEDIN, DONALD S , 72 64-70  
 WEED, WILLIAM A , JR , 67 391-395, 72 119-122  
 WEINER, HENRY E , 68 31-41, 594-602, 70 344-348  
 WEINBERG, EUGENE E , 67 503-508  
 WEINBERG, JOSEPH, 60 288-304  
 WEINER, ROBERT S , 74 729-738  
 WEINSHEL, MAX, 64 50-63  
 WEINSTEIN, S B , 72 345-355  
 WEISEL, WILSON, 61 474-482, 742-746, 71 573-583, 73 773-775  
 WEISER, ORMAN L , 69 58-64, 464-468, 73 117-122, 77 1023-1025  
 WEISER, RUSSELL S , 64 669-674, 68 564-574, 69 406-418  
 WEISS, CHARLES, 63 694-705  
 WEISS, DANIEL L , 75 954-957, 76 507-508, 78 793  
 WEISS, DAVID W , 73 781-784, 77 719-724, 79 813-815, 80 340-358, 495-509, 676-688  
 WEISS, WILLIAM, 62 160-169, 307-313, 64 64-70, 65 735-743, 69 396-405, 844, 72 268-273, 75 319-325, 76 897-898, 78 17-20, 79 537-540  
 WEISSMAN, HERMAN, 64 572-576, 73 853-867, 76 1088-1093  
 WELCH, EDWARD J , 67 94-100  
 WELLER, L E , 62 475-480  
 WELLS, A Q , 66 28-35, 69 479-494, 72 53-63  
 WELLS, WILLIAM F , 75 420-431  
 WERNER, CHARLES A , 63 49-61  
 WERNER, GEORGES H , 69 473  
 WERNER, WILLIAM A , 67 514-516  
 WERTMAN, DANIEL E , 77 32-38  
 WESSERMAN, EDWARD, 78 815-821  
 WEST, ANN F , 80 398-403  
 WHALEN, JOSEPH W , 71 382-389  
 WHARTON, DWIGHT J , 80 188-199  
 WHITCOMB, FRANCES C , 68 727-733, 71 762-764  
 WHITCOMB, WALTER H , 78 391-398  
 WHITE, ARTHUR C , 77 134-145, 80 12-18, 443-444  
 WHITE, F CLARK, 62 107, 72 274-296, 79 134-141  
 WHITE, ROBERT G , 70 793-805  
 WHITESIDE, ELEANOR S , 69 419-442  
 WHITFIELD, GEORGE B , 75 584-587  
 WHITNEY, JACK M , 76 852-861  
 WHITTAKER, CHARLES KEITH, 70 920-921  
 WHITEHART, JAMES L , 72 453-464  
 WHORTON, MERRILL C , 65 596-602  
 WIDELOCK, DANIEL, 67 598-603, 68 290-291, 734-738, 69 1022-1028, 70 349-359, 363-366, 728-733, 1042-1053, 71 305-307, 841-859, 72 143-150, 246-251, 74 293-296, 428-437, 75 41-52, 76 732-751, 78 788-792  
 WIER, JAMES A , 73 117-122, 75 921-937, 76 811-831, 77 749-763, 80 259-261, 569-574  
 WIESE, E ROBERT, 63 480-486  
 WIGGINS, MILTON L , 69 818-823  
 WILEY, L J , 79 541  
 WILKING, VIRGINIA N , 66 63-76  
 WILL, DRAKE W , 61 226-246, 76 435-450  
 WILLETT, HILDA POPE (*see also* POPE, HILDA), 80 404-409  
 WILLIAMS, JAMES H , 65 511-518, 519-522  
 WILLIAMS, JOHN H , JR , 72 107-116, 76 360-369  
 WILLIAMS, MARVIN L , 62 549-554  
 WILLIAMS, M HENRY, JR , 78 173-179, 80 689-699, 700-704  
 WILLIAMS, ROBERT O , 76 660-668  
 WILLIAMSON, JAMES, 77 623-643  
 WILLIS, GERTRUDE MITCHELL, 76 1049-1062  
 WILLIS, H STUART, 61 387-398, 62 (Supplement, July 76-79), 64 113-116, 66 95-98, 73 291-293, 74 793-795, 77 802-814  
 WILLIS, MYRON J , 69 234-240, 78 667-681  
 WILLISTON, ELIZABETH H , 59 336-353, 62 156-159, 481-483  
 WILMER, HARRY A , 69 847-851  
 WILSON, F JEAN, 65 187-193  
 WILSON, GEORGE C , 73 351-361  
 WILSON, GEORGE M , 78 604-609  
 WILSON, HENRY M , 68 615-621  
 WILSON, MICHAEL M , 65 187-193  
 WILSON, NORMAN J , 60 406-418, 704-705, 68 874-884  
 WILSON, RUSSELL H , 68 177-187, 70 296-303  
 WILT, KENNETH E , 77 62-72  
 WINDER, FRANK, 71 785-798, 73 779-780, 75 476-487  
 WINFIELD, DON L , 70 476-482  
 WINGO, CHARLIE F , 76 660-668  
 WINSTEN, SEYMOUR, 70 806-811, 74 59-67, 72-77  
 WINTER, WILLIAM J , 61 171-184  
 WINTERSCHIED, LOREN C , 67 59-73, 68 625-628  
 WISELOGLE, FREDERICK Y , 60 121-130  
 WITHERINGTON, DEATFR T , 71 892-893  
 WITTKOWER, ERIC D , 67 869-873, 71 201-219

WOIWOD, A J , 72 123-125  
 WOLD, DEWITT E , 74 445-453  
 WOLFSON, IRVING N , 67 103-105  
 WOLINSKY, EMANUEL, 59 221, 62 300-306, 64 87-101, 65 365-375, 754-758, 66 194-212, 68 65-74, 548-556, 70 367-369, 375, 714-727, 71 308-313, 73 72-78, 539-546, 768-772, 75 180-198, 510-513, 965-974, 76 497-502, 643-659, 77 168-171, 78 570-575, 80 269-273, 522-534  
 WOLOCZOW, H , 79 541  
 WONG, HARRY YOUMAN, 75 148-152  
 WOOD, LAWRENCE E , 69 227-233, 234-240, 73 917-929, 78 667-681  
 WOODBURY, JOHN W , 60 648-653  
 WOODHAM, GEORGE E , 75 949-953  
 WOODRUFF, C EUGENE, 59 391-401, 60 794-800, 61 269, 387-398, 62 555, 63 140-149, 64 620-629, 66 151-160, 67 286-291, 292-298, 68 583-593, 69 451-454, 70 518-520, 533-534, 71 766, 75 975-986, 80 445  
 WOODS, FRANCIS M , 68 902-911  
 WOODWARD, THEODORE E , 71 592-595  
 WOOLF, A L , 59 311-316  
 WOOLF, C R , 74 511-532, 80 705-715  
 WOOLF, VICTOR F , 59 679-686  
 WORKMAN, JOHN M , 75 823-827  
 WORSSAM, ANTHONY R H , 73 726-734  
 WORTMAN, H C , 60 520-523  
 WRIGHT, GEORGE W , 60 706-714  
 WRIGHT, JEANNE E , 59 494-510  
 WRIGHT, KENNETH W , 67 652-656, 74 128-135, 79 72-77  
 WRIGHT, NOBLE M , 74 638-640  
 WRIGHT, R R , 79 212-220  
 WRINKLE, CAROLYN K , 66 99, 69 599-603  
 WU, JACK FOY, 63 710-713  
 WU, NANCY, 71 693-703  
 WUNDERLICH, GOOLOO S , 80 371-387  
 WYATT, JOHN P , 80 (Supplement, July 94-103)  
 WYBORNEY, V J , 75 854-855  
 WYLIE, ROBERT H , 61 465-473, 74 351-357  
 WYNN-WILLIAMS, N , 69 724-732

## Y

YALE, HARRY L , 65 357-364, 67 354-365, 366-375  
 YAMAMOTO, MASAKUNI, 79 371-373  
 YAMAMURA, YOSHIHIRE, 79 738-745  
 YAMAMURA, YUICHI, 75 99-104, 77 482-491, 79 738-745, 80 240-248, 535-542, 911  
 YAMAURA, KENJI, 80 543-553  
 YANG, STEPHEN C H , 61 648-661  
 YANNAKOS, D , 72 527-536  
 YANNITELLI, S A , 59 391-401, 60 794-800  
 YARD, ALLAN S , 73 956-959

YASAKA, SHIGERU, 75 99-104  
 YATER, WALLACE W , 71 904-924  
 YATES, J LEWIS, 69 216-226  
 YEAGER, ROBERT L , 65 519-522, 523-546, 635-636  
 YEGIAN, DIRAN, 61 483-507, 63 96-99, 64 81-86, 65 181-186, 66 44-51, 629-631, 68 557-563, 71 860-866, 72 539-542, 73 586-588, 75 781-792, 76 272-278  
 YERUSHALMY, J , 61 443-464, 64 225-248, 249-255  
 YIN, S C , 74 417-427, 468-470  
 YOSHIMURA, TETSUYA, 80 543-553  
 YOUATT, JEAN, 78 806-809  
 YOUMANS, ANNE STEWART, 63 25-29, 64 534-540, 541-550, 69 790-796, 72 196-203, 73 764-767, 80 750-752, 753-756  
 YOUMANS, GUY P , 59 336-352, 61 407-421, 569-577, 62 156-159, 62 481-483, 63 25-29, 64 534-540, 541-550, 66 416-435, 486-496, 69 790-796, 72 196-203, 73 637-649, 764-767, 75 280-294, 76 616-635, 77 301-310, 450-461, 462-472, 80 153-166, 750-752, 753-756  
 YOUNG, A C , 73 330-337  
 YOUNG, HENRY, 73 868-881  
 YOUNG, J M , 67 385-390  
 YOUNG, R C , 79 468-473  
 YOUNG, ROBERT J , 72 204-209, 76 225-231  
 YU, PAUL N G , 62 29-44, 79 265-272  
 YUE, WEN Y , 78 899-905

## Z

ZAHN, DANIEL W , 59 636-642, 69 351-369, 74 445-453, 75 644-647  
 ZAJCEW, W , 78 411-425  
 ZAPPASODI, PETER, 72 297-329, 79 152-179, 180-203  
 ZARAFONETIS, CHRIS J , 71 220-227  
 ZAROWITZ, HAROLD, 60 801-807  
 ZASLY, LOUIS, 74 624-632  
 ZEIDBERG, L D , 65 111-127, 70 360-362, 1009-1019, 75 111-121  
 ZIEVE, LESLIE, 64 159-169  
 ZIMMERMAN, H M , 62 586-593  
 ZINNEMAN, HORACE H , 74 773-782, 76 247-255, 78 832-838  
 ZINS, EUGENE I , 60 206-211  
 ZISKIND, JOSEPH, 80 (Supplement, July 104-112)  
 ZISKIND, MORTON M , 68 382-393  
 ZITRIN, CHARLOTTE MARKER, 74 15-28, 76 256-262  
 ZOHRAN, LENORE R , 78 173-179, 80 689-699, 700-704  
 ZORINI, A OMODEI, 78 485-487  
 ZOUMBOLAKIS, D , 72 527-536, 73 964-965, 74 (Supplement, August 197-208)  
 ZUCKERMAN, ANNE, 64 318-321  
 ZWERLING, HENRY B , 64 225-248, 249-255



# INDEX OF SUBJECTS

## A

- Abortion and tuberculosis, 70 49-60
- Abscess(es)
  - cold, spontaneous, of chest wall, 62 (Supplement, July 48-67)
  - pulmonary
    - acute, 61 474-481, 69 673-681
    - pancreatic desoxyribonuclease in, 76 1-21
    - in tularemia, (case reports) 65 627-630
- Abstracting philosophy, (editorials) 62 446-448
- (4)-Acetylamino benzal thiosemicarbazone *See* Thiosemicarbazones
- Achalasia, (case reports) 76 480-490
- Acid(s)
  - amino
    - metabolism, detected in urine from tuberculous patients, (Notes) 76 867-870
    - relation to problem of host resistance to tuberculosis, (Notes) 66 378-380
    - of urinary excretion
      - in normal subjects on controlled diets, 60 439-447
      - in tuberculous subjects on controlled diets, 60 448-454
  - ascorbic
    - tuberculin-inhibitory properties and inhibition of tubercle bacilli by urine, 69 406-418
    - in tuberculosis, 64 381-393
  - fatty
    - in calf lung, effect on tubercle bacilli, 75 630-637
    - in rabbit tissue, resistance of tubercle bacilli, 69 710-723
  - heterocyclic, hydrazides and derivatives in experimental tuberculosis, 67 366-375
  - isonicotinic, hydrazide *See* Isoniazid
  - kojic, as inhibitor of tubercle bacilli, 61 739-741
  - para-aminosalicylic *See* Para-aminosalicylic acid
  - phthienic, and related acids, cellular reactions, 65 655-672
- Acid-fast bacilli *See* Bacilli and Tubercle bacilli
- Acidosis, respiratory, induction by oxygen breathing, 77 737-748
- Acoustic basis of chest examination, 72 12-34
- ACTH *See* Hormones, corticotropin
- Actinomycetales *See* Fungi
- Actinomycosis *See* Mycoses
- Addison's disease, with histoplasmosis and pulmonary tuberculosis, (case reports) 72 675-684
- Adenitis, tuberculous
  - mediastinal and hilar, 76 799-810
  - treatment of, report by ATS Committee on Therapy, 68 302-305
- Adenoma *See* Tumors
- Adenomatosis *See* Tumors, adenomatosis, and carcinoma, alveolar
- Adolescents, nutrition and tuberculosis in, 74 (Supplement August, 173-183)
- Adrenocortical function
  - and tuberculin sensitivity, 73 795-804
  - in tuberculosis, pulmonary, 64 630-644, 66 364-372
    - during isoniazid therapy for, 70 841-851
    - relationship with stress and, 69 351-369
- Adrenocorticotrophic hormone *See* Hormones, corticotropin
- Aerosol, amphotericin B used as, (Notes) 80 441-442
- Agar diffusion
  - precipitation techniques, in determining mycobacterial antigenic relationships, 73 637-649
  - double, in tuberculosis, 77 462-472
- Aged persons
  - resection in, 73 40-51
  - tuberculin sensitivity in, 75 461-468
  - skin, 77 323-328
- Agglutination, collodion, effect of histoplasmin skin tests, 66 588-593
- Agitator, for bacteriologic specimens, (Notes) 70 176-177
- Agranulocytosis
  - due to amithiozone, (case reports) 65 339-343
  - during streptomycin treatment of military tuberculosis, 59 317-324
- Air *See also* Pulmonary function
  - embolus during pneumoperitoneum, (case reports) 72 537-538
  - flow, physics of, in emphysema, 80 (Supplement, July 123-125)
  - hygiene in tuberculosis, 75 420-431
  - pollution and bronchitis, (editorials) 80 582-584
  - travel in tuberculosis, 61 678-689
  - velocity index, 62 17-28
  - ways, chronic obstruction of, pulmonary diffusion in, 71 249-259
- Air-borne infection in rabbits, 73 315-329
- Alaska, histoplasmin sensitivity of natives, (Notes) 79 542
- Alcohol, effect on tubercle bacilli in sputum, 68 419-421
- Alcoholism in the tuberculous before and during hospitalization, (editorials) 79 659-662
- Aldinamide<sup>®</sup> *See* Pyrazinamide

- Allergens, acid fast, methods for comparison of potency, 60 131-139
- Allergy (ies)  
 effect of isoniazid on, 74 (Supplement, August 197-208)  
 in emphysema, 80 (Supplement, July 181-183)  
 to isoniazid, (case reports) 74 783-792  
 to para-aminosalicylic acid, 65 235-249  
 relationship to gross lung disease, 78 226-234
- Allescheria boydii* See Fungi
- Alloxan-induced diabetes in albino rats, compared with cortisone-treated tuberculosis, 65 603-611
- Alpha-ethyl-thioisonicotinamide, experiments on antituberculosis activity of, 79 1-5
- Alveolar cell carcinoma See Tumors, carcinoma
- Alveolar proteinosis, pulmonary See Alveolus
- Alveolus(i)  
 chronic emphysema of, in horse, 80 (Supplement, July 141-143)  
 pulmonary proteinosis of, (case reports) 80 249-254  
 respiratory surface, effective, and other pulmonary properties in normal persons, 70 296-303
- Amberson, J Burns, lecture, 74 821-829, 76 931-941, 78 499-511, 80 315-325  
 notes on (ATS), 74 980-983
- Ambulatory patients  
 tuberculous  
 chemotherapy in, 70 1030-1041, 75 41-52  
 with "open-negative" syndrome, 78 725-734
- American Trudeau Society  
 Amberson lectures, opening remarks on, 74 980-983  
 Annual Meetings, abstracts of medical papers presented at, (1958) 78 285-328, (1959) 79 822-850  
 award of the Trudeau medal, 67 114-119, 68 808-811, 72 559-565, 74 647-649, 76 1112-1116, 78 957-959  
 award of the Will Ross medal for 1954, 72 566-568  
 changes ahead, (editorials) 75 648-649  
 Charles J Hatfield lecture, introduction, 76 920-921  
 coronary arterial disease, symposium, 71 904-924
- DIAGNOSTIC STANDARDS AND CLASSIFICATION OF TUBERCULOSIS of National Tuberculosis Association, history of, 65 494-504
- formula for determining irregular discharge rates, 78 959-960
- manual for consecutive case conference (Pembine type), 79 258-262
- methods for determining susceptibility of tubercle bacilli to streptomycin, dihydrostreptomycin, and PAS, 65 105-108
- necrology, 67 122, 705, 75 698, 77 874, 80 122
- notices, 63 230, 623-624, 64 125-126, 223, 476, 579-582, 65 109-110, 219-220, 504, 652-653, 66 117, 260, 389, 508, 649, 781-782, 67 120-121, 270-271, 396-397, 550, 574, 68 306, 502, 654, 837, 972, 69 148, 317, 477, 655, 858, 1071, 70 380, 545, 759, 952, 1111, 71 160, 332, 464, 607, 771, 925, 72 140, 256, 417, 710, 73 156, 313, 449, 74 167, 307, 484, 652, 984, 75 168, 355, 528, 697, 1018, 76 166, 328, 513, 713, 928, 1117, 77 200, 373, 560, 728, 875, 1036, 78 150, 329, 496, 659, 814, 960, 79 118, 263, 397, 549, 697, 851, 80 123, 282, 455, 597, 764, 924
- obituaries, 67 398, 551, 68 154, 69 649, 70 187, 543, 71 326, 73 310, 790, 74 163, 650, 818, 75 352, 859, 76 326, 711, 927, 77 371, 78 146, 490, 79 118, 394, 695, 80 120, 452, 453, 921
- organization and committee structure,  
 1953-1954, 69 131-142  
 1954-1955, 71 148-159  
 1955-1956, 73 145-151  
 1956-1957, 75 157-167  
 1957-1958, 77 191-199  
 1958-1959, 79 108-117
- panel discussions  
 on changing concepts and modern treatment of tuberculosis, 70 930-948  
 on chemotherapy of tuberculosis, 67 680-697  
 on giving pneumoperitoneum or pneumothorax, 68 954-971  
 on present concepts of antimicrobial therapy in pulmonary tuberculosis, 68 819-836  
 on survival and revival of tubercle bacilli in healed tuberculous lesions, 68 477-495  
 on therapy of miliary and meningeal tuberculosis, 68 636-653
- Pembine Conferences, reports on  
 Eighth, 65 786-791  
 Ninth, 68 496-501  
 Tenth, 70 184-186  
 Eleventh, 72 137-139  
 Twelfth, 73 973-975  
 Thirteenth, 76 164-165
- postgraduate courses in pulmonary disease, 59 111-112
- preliminary program of annual meeting, medical sessions, (1958) 77 553-559, (1959) 79 387-393
- present objectives and policies in the field of medical education, the role and

## American Trudeau Society

- responsibility of the Committee on Medical Education, 69 113-117
- production and distribution of BCG vaccine in the U. S. A., 65 647-648
- reports
  - of Clinical Subcommittees
    - on current status of drug therapy in tuberculosis, 61 137-149
    - on German experience with thiosemicarbazone, 61 145-157
    - on streptomycin in the treatment of tuberculosis, 53 105-110
  - of Clinical and Laboratory Subcommittees, 63 197-200, 65 100-108
  - of Committee on Medical Research, 1951-1952, 64 503-505, 1952-1953, 68 512-516
  - of Committee on Therapy and of Laboratory Subcommittee of Committee on Medical Research, 65 351-355
  - of Committee on Therapy to Committee on Medical Research, 64 641-646, 68 616-649, 69 313-315, 69 1068-1069, 70 340-342
  - of Director of Medical Education, 70 1105
  - of Executive Secretary, 70 1107-1109
  - of Fellowship Board of Committee on Medical Research, 1951-1952 64 597-597, 1952-1953, 68 516-518
  - of Interim Committee on Diagnostic Standards, 68 150-152
  - on isoniazid toxicity, by Committee on Therapy, 65 302-305
  - of the Laboratory Subcommittee of Committee on Medical Research and Therapy, and of Subcommittee on Evaluation of Laboratory Procedures of Committee on Revision of Diagnostic Standards, 61 274-298
  - of Laboratory Subcommittee to Committee on Medical Research, 66 647-648, 68 951-953, 69 316
  - on projects for the recovering tuberculosis patient
    - in some European countries, 66 101-108
    - in the United States, 67 698-703
  - on pyrazinamide, by Committee on Therapy, 75 1012-1015
  - on resections of residual necrotic lesions, by Committee on Therapy, 67 268
  - of (Dr. H. McLeod) Riggins, chairman of Committee on Medical Research and Therapy, read at the Annual Meeting, April 21-28, 1950, 62 556-561
  - on sections of the American Trudeau Society, 70 1107-1109
  - by Subcommittee on Clinical Classification of
    - Committee on Revision of Diagnostic Standards, on classification of pulmonary tuberculosis, 61 760-763
    - of Subcommittee on Pulmonary Function Tests, 62 451-454
    - on treatment of tuberculous lymphadenitis, by Committee on Therapy, 70 949-951
    - at Veterans Administration Thirteenth Conference on Chemotherapy of Tuberculosis, 69 854-857
  - request for data on effects of cortisone corticotropin on tuberculosis in humans, by Committee on Therapy, (correspondence) 64 471-472
  - statements
    - on BCG, 69 681-682
    - role in prevention of clinical tuberculosis, 78 145
    - by Committee on Administrative Problems, recommendations for use of vacant tuberculosis beds, 76 922-923
    - by Committee on Medical Research
      - clinical significance of *in vitro* determinations of streptomycin susceptibility and resistance, 65 103-105
      - criteria for "negative" sputum in patients following antimicrobial therapy, 65 102-103
    - by Committee on Radiation Effects, chest roentgenogram and chest roentgenographic surveys related to X-ray radiation effects and protection from radiation exposure, 80 115-117
    - by Committee on Therapy
      - antimicrobial therapy of tuberculosis, 72 408-416, 78 656-658
      - BCG in prevention of clinical tuberculosis, 78 145
      - bed rest in treatment of tuberculosis, 69 1069-1070
      - cycloserine, 75 1016-1017
      - effect of cortisone and/or corticotropin on tuberculous infection in man, 66 254-256
      - genitourinary tuberculosis, 72 413-415
      - in female genital tract, 75 524-527
      - indications for adjuvant corticotropin and corticosteroid therapy in tuberculosis, 76 708-710
      - need for rest therapy in connection with long courses of drug treatment for pulmonary tuberculosis, 67 679
      - the "open negative" problem, 80 118-119
      - present status of excisional surgery in treatment of pulmonary tuberculosis, 72 416

*American Trudeau Society statements, cont*

- present status of skeletal tuberculosis, 71 811-817
- problem of so called "good chronic" case of pulmonary tuberculosis, 61 613-646
- recommended standards for home care of patients with tuberculosis, 78 655-656
- role of Committee on Therapy in the American Trudeau Society, 66 611-616
- treatment of tuberculous meningitis, 70 756-758
- by Committees on Therapy and on Administrative Problems, acceptable standards in the treatment of tuberculosis, 73 607-608
- by Executive Committee, the chest roentgenogram and chest roentgenographic surveys related to X-ray radiation effect and protection from radiation exposure, 77 203-208
- by Laboratory Subcommittee, hypopharyngeal (laryngeal) swabbing for the cultural diagnosis of pulmonary tuberculosis, 73 970-972
- by Subcommittee on Pulmonary Function, 73 152-155
- streptomycin tuberculosis research project, 59 140-167
- tuberculosis hospital medical and administrative standards, 72 699-709
- tuberculosis mortality among residents of large cities (1947-1949), 66 109-116
- "Tuberculosis A World-Wide Problem" conference, papers from (November 18, 1958), 79 684-694
- Amines, primary, simple, *in vitro* and *in vivo*, 61 407-421
- Amino acid *See* Acids
- (4)-Amino-4' B hydroxyethylaminodiphenyl sulfone *See* Hydroxyethyl sulfone
- Aminophylline as bronchodilator agent, 77 729-736
- Amithiozone *See* Thiosemicarbazones
- Amphotericin B
  - as aerosol, (Notes) 80 441-442
  - serum concentrations in man, (Notes) 77 1023-1025
- Amylase, content of pleural fluid in pancreatitis and other diseases, 79 606-611
- Anaphylaxis, to viomycin, (case reports) 75 135-138
- Anemia
  - aplastic, following use of streptomycin-PAS, (case reports) 68 455-457
  - hemolytic, following treatment with PAS, (case reports) 76 862-866
  - sickle cell, and hepatic tuberculosis, (case reports) 67 247-257
  - and tuberculosis, 65 735-743
- Anergy, in tuberculous patients
  - changes in tuberculin sensitivity when treated with antimicrobial therapy, 67 286-291
  - and prolongation of life, 67 292-298
- Aneurysm, Rasmussen's, in pulmonary tuberculosis, 60 589-603
- Angiocardiography in artificial pneumothorax, 62 353-359
- Angiography in advanced pulmonary tuberculosis, 71 810-821
- Angiopneumography and bronchography in tuberculous fibrothorax, 73 61-71
- Anomaly
  - of the lung and bronchial tree, 64 686-690
  - vascular, and lung cysts, (case reports) 71 573-583
- Anorexia, treatment with insulin, 60 25-31
- Anthracite coal miners *See* Pneumoconioses
- Anthracosilicosis *See* Pneumoconioses
- Antibacterial agents
  - active against tubercle bacilli in seed plants, 62 475-480
  - and isoniazid resistance, (Notes) 68 283
- Antibiotics *See* Antimicrobials and specific names of drugs
- Antibody(ies) *See also* Hemagglutination
  - antituberculous
    - masked, 72 345-355
    - studies, 72 210-217
  - circulating, to tuberculosis, demonstration of clinical studies, 75 954-957
  - technique, 75 949-953
  - hemagglutination test, 65 194-200
  - and its hemolytic modification in tuberculosis, 65 194-200
  - slide test modifications, against tubercle bacilli, 63 667-671
  - interference by tuberculoprotein and polysaccharide in pulmonary tuberculosis, 73 547-562
  - lung-specific, in rabbits, 78 259-267
  - protective, in tuberculosis, 76 256-262
- tuberculous
  - by agar diffusion, 74 229-238, 239-244
  - in human serum, 74 239-244
  - in rabbit serum, 74 229-238
- Antigen(s)
  - BCG extract, from sheep erythrocytes, 75 958-964
  - fungal, sensitivity to, in students, 73 620-636
  - mycobacterial, serologic investigations of, 73 563-570, 571-575, 74 756-763, 764-772, 75 958-964
  - PPD and others, prepared from atypical acid-fast bacilli and *Nocardia asteroides*, 79 284-295

- Antituberculous compounds, *in vitro* activity of, 66 219-227
- Antituberculous drugs. *See also* Chemotherapy, Drugs, and specific names of drugs  
bactericidal activities, 71 (supplement, August 109-116)
- Antituberculosis treatment, effectiveness, tested by direct culture of bacilli in patient's blood, (Notes) 80 85-88
- Aorta, abdominal  
hemorrhage into jejunum through tuberculous lymph nodes, (case reports) 65 210-211
- tuberculous arteritis of, with rupture into duodenum, (case reports) 60 801-807
- Aplastic anemia. *See* Anemia
- Appendicitis  
during pneumoperitoneum treatment, 61 353-354
- tuberculous, 61 182-191
- Arcana of tuberculosis. Parts I and II, 78 151-172, Part III, 78 426-453, Part IV, 78 583-603
- Armed Forces, Selective Service registrants with tuberculosis, 80 795-805
- Army, streptomycin regimens in, study of, (July 1946-April 1949) 60 715-754
- Arterial alveolar oxygen tension gradient, in pulmonary disease, 69 71-77
- Arteriosclerosis, obscure pulmonary, and right heart failure (Ayerza's disease), cardiac cirrhosis with, (case reports) 70 1083-1091
- Arteritis, tuberculous, of aorta, with rupture into duodenum, (case reports) 60 801-807
- Artery (ies)  
coronary, surgical approach to disease of (symposium), 71 991-994
- innominate and subclavian aneurysms, (case reports) 70 709-705
- pulmonary  
aneurysm in circulation of, (case reports) 70 641-651
- pressure, and frequency of postprimary pulmonary tuberculosis, 78 536-546
- Ascorbic acid. *See* Acid
- Asparaginase of mycobacteria, (Notes) 70 920-921
- Asparagine, utilized by *M. tuberculosis* for growth, 68 127-135
- Aspen. *See* United States, Colorado
- Aspergillus fumigatus*. *See* Fungi
- Aspergillus* infestation. *See* Fungi
- Asphyxia, fatal, from Lucite plumbage, 61 422-425
- Atelectasis  
basal linear, after phrenic nerve interruption, 65 88-92
- segmental, in children with primary tuberculosis, 70 597-605
- Atherosclerosis, coronary (symposium), 71 994-994
- Aureomycin. *See* Chlorotetracycline
- Auscultation, 60 639-647  
acoustic basis of chest examination, 72 12-34
- Ayerza's disease, and cardiac cirrhosis, (case reports) 70 1083-1091
- ## B
- B663, *See* Phenazine
- Bacillus(i)  
acid fast  
atypical, 73 351-361, (Notes) 80 134-437
- PPD and other antigens prepared from, 79 284
- in sputum of patient with pulmonary lesions, 75 199-222
- chromogenic  
from human sources, (correspondence) 73 601-603
- culture, 65 278-288
- hypersensitivity, 65 302-315
- pathology, 65 289-301
- oxygen requirements, 69 604-611
- response to antimicrobial agents on glycerol-blood agar medium, (Notes) 72 119-122
- susceptibility to chemotherapy, (Notes) 76 697-702

*Bacillus(s), acid fast, cont*

- cultural studies, 76 103-107, 108-122
- human, nontuberculous, penicillin susceptibility in, (Notes) 75 675-677
- from human sources, (correspondence) 72 695-698
- methods of testing virulence, 62 632-637
- nonpathogenic for guinea pigs, 73 351-361, (correspondence) 74 478-480
- nontuberculous, from humans, bacteriologic studies, (Notes) 76 683-691
- report of panel, 72 866-870
- sputum examination, 59 449-460
- "wax" in guinea pig sensitization, 69 241-246
- "yellow" in human infection, 73 917-929
- Calmette-Guérin *See* BCG, Tubercle bacilli
- tubercle *See* Tubercle bacilli
- yellow, pathogenicity of, 71 74-87
- Bacterial resistance, incidence, encountered with tuberculosis chemotherapy regimens employing isoniazid and isoniazid-streptomycin, (Notes) 67 106-107
- U S Public Health Service cooperative clinical investigation, (editorials) 70 739-742
- Bacteriophage, temperate, from *M. butyricum*, 80 232-239
- Bacterium(a)
  - acid-fast, metabolism of
    - Krebs cycle in acetate oxidation pathways of, 71 266-271
    - and *Mycobacterium*, 71 260-265
  - transformation, not induced by desoxyribonucleic acid, (Notes) 80 911
- Baldwin, Edward R., (editorials) 62 (Supplement, July 1-2)
- Ballistocardiogram, after artificial pneumoperitoneum, in chronic pulmonary diseases, 66 52-57
- Barbiturates, effect on isoniazid toxicity, (Notes) 66 100-103
- BCG
  - allergy, isoniazid effect, 77 232-244
  - American Trudeau Society statements, 60 681-682, 78 145
  - crude extracts, biologic activity, (Notes) 78 939-943
  - effect of bile, 59 102-105
  - extract antigens in detection of homologous antibodies, 74 756-763, 764-772
  - fatal tuberculosis induced by, 70 402-412, (correspondence) 71 321-323, 73 301-305
  - harvesting and dispensing apparatus, (Notes) 63 613-614
  - immunization, lack of circulating antibodies after, by globulin titration, (Notes) 78 793
  - immunizing activity, affected by isoniazid, (Notes) 75 650-655
  - immunizing properties compared with an isoniazid-resistant mutant of *M. tuberculosis*, (Notes) 70 527-530
  - infection
    - in guinea pig, cortisone in, 69 511-519
    - from injection, (correspondence) 72 869-870
  - inoculation in children, reactions, 74 (Supplement, August 32-42)
  - and irradiated antituberculosis vaccine, in experimental tuberculosis in guinea pigs, 67 341-353
  - method of obtaining, (correspondence) 79 105
  - and *M. tuberculosis*, metabolism of isoniazid by, (Notes) 78 806-809
  - preservation by freeze-drying, (Notes) 65 344-346
  - production, new method, (Notes) 64 698-701
  - report of ad hoc advisory committee to Surgeon General (1957), 76 726
  - role in prevention of clinical tuberculosis, 78 145
  - specificities of aqueous and saline extracts, 73 563-570, 571-575
  - standardization, (correspondence) 65 641
  - strain, cultivation of, (Notes) 78 934-938
  - studies, (Notes) 68 462-466
  - substrains, differential characteristics *in vivo* and *in vitro*, 74 655-666, 667-682, 683-698, 699-717
  - Tice strain, (correspondence) 75 692-693
  - tuberculin reaction variation after, 60 541-546
  - use and value, 76 715-525
  - vaccination
    - community trials, 77 877-907
    - correlation of tuberculin reaction with pulmonary lesions in persons with and without, 68 713-726
  - cortisone and isoniazid in, 76 263-271
  - effect
    - and hyaluronidase, 64 442-447
    - on mice infected with tuberculosis, 68 451-454
  - of guinea pigs
    - by multiple puncture method, 60 547-556
    - sonic fragility of leukocytes from, 79 323-328
  - in humans, followed by hemagglutination reaction, 66 58-62
  - immunologic aspects, (editorials) 60 670-674
  - as index of familial susceptibility to tuberculosis, 69 383-395
  - and influence on tuberculin test, 72 35-52
  - lymphatic calcification after, 73 239-245
  - and measles, (case reports) 72 228-230
  - of mice, 75 624-629

## Bacterial count

- microscopy and culture of *M. tuberculosis* in, 70 481-491
  - in Panama, (Notes) 67 522-525
  - properties, and isoniazid resistant mutant in guinea pigs, (Notes) 75 656-658
  - pulmonary lesions in persons with and without, 68 695-712
  - in rabbit tissues, 72 310-311
  - in sarcoidosis, 62 408-417
  - in silicosis, 62 455-471, 69 763-769
  - in Sweden, (correspondence) 70 678-679
  - tuberculin
    - allergy after, 70 1061-1062
    - compared in persons with and without, 70 71-90
  - fraction
    - purified, from unheated cultures, 69 300-303
    - for testing vaccinated subjects, 66 335-341
    - and sensitivity in Hong Kong, 76 215-221
    - of tuberculous children, serum protein electrophoretic pattern and Middlebrook-Dubos titer, (Notes) 79 522-524
    - and Vole, 71 (Supplement, August 13-50)
  - vaccine
    - bacterial count, vital staining method, (Notes) 78 785-787
  - effect
    - of age and temperature, 68 96-102
    - of time and temperature on antigenic potency, 70 873-880
  - fresh, frozen, and dry, antigenic activity, 63 85-95
  - and hyaluronidase, synergistic effect in guinea pigs, 68 188-198
  - progress toward standardization, (editorials) 79 80-82
  - viability, (Notes) 63 711-716
    - influence of methods of preparation, (Notes) 61 695
    - new method of counting organisms, (Notes) 79 816-817
  - virulence, 59 567-588
- Bed rest, modified
- in minimal tuberculosis, 61 809-825, 67 401-420
  - in pleural effusion, 67 421-431
  - on recovery from pulmonary tuberculosis, and physical activity, 75 359-409
- Beds, hospital, for tuberculous patients, ATS statement on, 76 922-926
- Bellevue Hospital (New York City), chest service (Amberson Lecture), 74 821-829
- Bellows apparatus in pulmonary function studies, 80 721-731
- Benemid® See Probenecid
- Benadonium chloride in isolation of *M. tuberculosis*, (Notes) 71 281-288
- resistant to, 70 312-319
- in tuberculosis bacteriology, (Notes) 80 912-913
- Benzoate, action in tubercle bacilli, 69 705-709
- Benoxyl PAS
  - inhibiting isoniazid inactivation in man, 80 26-37
  - metabolism, biochemical aspects, (Notes) 75 1003-1006
- Beryllium See Pneumoconiosis
- Bile, effect on BCG, 59 102-105
- Biochemistry in analysis of virulence of tubercle bacilli, 80 535-542
- Biology of tuberculosis, 68 1-8
- Biopsy (ies)
  - bronchial, preoperative, in pulmonary tuberculosis, 78 S39-S47
  - laryngeal, during chemotherapy, 69 247-260
  - of lung, 71 668-677
  - needle, of the parietal pleura in tuberculosis, 78 17-20
  - pericardial, 75 469-475
  - pleural, for effusions, 78 S-16
  - scapular node, 68 505-522
- Blastomycosis dermitidis See Ungi
- Blastomycosis See Mycoses
- Blebs, subpleural, surgery of, 79 577-590
- Blood See also Serology, Serum cells
  - red See Erythrocytes
  - white See Leukocytes
- of cold blooded animals, mycobacteria in, 77 823-838
- direct culture of bacilli in, as drug therapy test, (Notes) 80 85-88
- flow, through nonventilated portions of lung, 68 177-187
- iodine, effect of Dionasil® on, 77 181-183
- layering, in dog heart, 70 570-576
- media, for culturing tubercle bacilli, 64 551-556
- PAS in, 76 1071-1078
  - buffered, concentration studies, (Notes) 72 543-547
  - effect of probenecid on, 66 228-232
- pyrazinimide spectrophotometric determination in, 75 105-110
- serum
  - concentrations, attained with PAS ascorbate, 76 880-887
  - in pulmonary tuberculosis, protein-bound carbohydrates of, 75 793-806
- vessels, histologic study of, in resected tuberculous lungs, 64 489-498
- "Bluing" phenomenon, contamination source in tubercle bacilli cultures, (Notes) 80 95-99

- Body build, in relation to tuberculosis morbidity, 76 517-539
- Boeck's sarcoid *See* Sarcoidosis
- Bone  
grafts, homogenous, ribs from thoracoplasty as possible source, 63 210-212  
marrow, tubercle bacilli in, 63 346-351  
tuberculosis, in children with primary and miliary tuberculosis, 75 897-911
- BOOKS
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JACOB JESSE SINGER, 63 494
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390
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AND L HENRY GARLAND, 74 304
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seit 100 Jahren By G DOMAG, 79  
682
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*et al*, 68 472
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361
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129
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tion Bronchologique By JEAN  
IONNOU, L DUCHET-SUCHAUX, AND  
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74 304
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zation of the Tuberculous By  
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- Sandoz Atlas of Haematology, 72 134
- Sectional Radiography of the Chest By IRVING J KANE, 68 944
- Segmental Anatomy of the Lungs By EDWARD A BOYDEN, 75 349

*Books, cont*

- Selected Experiments in Medical Microbiology  
By STEWARD M. BROOKS, 79 107
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- Social-Medical Investigations on Tuberculosis in the County of Hordaland By K. ENGBAL, 77 725
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- The Therapy of Skin Tuberculosis Translated and revised by ERNEST A. STRAKOSCH, 73 417
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- Thoracic Surgery By RICHARD H. SWEET, 63 725, 70 378
- Thoracic Surgery and Related Pathology By GUSTAF E. LINDBSKOG AND AVERILL A. LIEBOW, 70 179
- Thoracic Surgical Patient By LEW A. HOCHBERG, 69 129
- Topographische Ausdeutung der Bronchien im Röntgenbild By CLAUD ESSER, 77 189
- Tracheotomy A Clinical and Experimental Study By THOMAS G. NELSON, 79 256
- Treatment of Respiratory Emergencies Including Bulbar Poliomyelitis By THOMAS C. GALLOWAY, 68 943
- Tubercle Bacillus and Laboratory Methods in Tuberculosis By M. A. SOLTYS, C. A. ST. HILL, AND I. ANSELL, 68 475
- Tubercle Bacillus in the Pulmonary Lesion of Man By GEORGES CANETTI, 72 555-558
- Die Tuberkulosebekämpfung in der Schweiz Edited by H. BIRKHAUSER, 72 557-558
- Tuberculose Primaire Chez l'Enfant By RAYMONDE GRUMBACH, 74 812
- Tuberculose Pulmonaire et Pleurale By PIERRE-BOURGEOIS, 70 926
- Tuberculosis *British Medical Bulletin*, vol 10, no 2, 1954 Edited by J. G. SCADDING, 71 324

*Books, cont*

- Tuberculosis A Global Study in Social Pathology By JOHN B McDUGALL, 63 493
- Tuberculosis in Animals and Man A Study in Comparative Pathology By JOHN FRANCIS, 79 682
- Tuberculosis and Aspiration Liver Biopsy Its Clinical Significance in Diagnosis and Therapy By A J CH HAEX AND CORNELIA VAN BEEK, 72 557
- Tuberculosis in Childhood and Adolescence By F J BENTLEY, S GRZYBOWSKI, AND B BENJAMIN, 71 605
- Tuberculosis Classification Pathogenesis and Management By MILOSH SEKULICH, 73 143
- Tuberculosis in History By LYLE S CUMMINGS, 61 592
- Tuberculosis in Ireland Report of the National Tuberculosis Survey MEDICAL RESEARCH COUNCIL, 72 405
- Tuberculosis Nursing Instruction in Universities for Public Health Nursing Students By JEAN SOUTH, 67 881-882
- Tuberculosis in Obstetrics and Gynecology By GEORGE SCHAEFER, 75 349-350
- Tuberculosis Treated with Streptomycin By E T BERNARD, B KREIS, AND A LOTTE, 62 228
- Tuberculosis in White and Negro Children, vol I The Roentgenologic Aspects of the Harriet Lane Study By JANET B HARDY, 78 952
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- Tumeurs Broncho-Pulmonaires Exposés Anatomiques By A POLICARD *et al*, 74 645
- Tumors of the Lungs and Mediastinum By B M FRIED, 80 113
- Über den Einfluss von Physikalischen und Chemischen Faktoren auf die Cytologie der Tuberkelbazillen und Anderer Mykobakterien By WERNER ROTH, 79 148
- Unsere Erfahrungen über die Moderne Behandlung der Milartuberkulose und der Meningitis Tuberculosa im Kindesalter By J R WEBER AND K KURHN, 78 135
- Vaccination Against Tuberculosis By L ŠULA and co workers, 74 160
- Vers la Médecine Sociale By RENÉ SAND, 60 116-117
- Veterans Administration Hospitals Number, the Medical Clinics of North America, January, 1959, The Major Pulmonary Diseases BENJAMIN B WELLS AND MARC J MUSSER, Consulting Editors, 80 762
- When Doctors Are Patients By MAX PINNER AND BENJAMIN F MILLER, 66 636
- White Plague By RENÉ AND JEAN DUBOS, 68 803
- Wish I Might By ISABEL SMITH, 73 308
- X-Ray Diagnosis of Chest Diseases By Coleman R Rabin, 68 298
- Yearbook of Drug Therapy Edited by HARRY BECKMAN, 80 919-920
- The Year Book of General Surgery—1958-1959 Series Edited by MICHAEL E DEBAKEY, 80 591-595
- You and Tuberculosis By JAMES E PERKINS AND FLOYD M FELDMAN, in collaboration with RUTH CARSON, 67 547
- You're Human, Too! By ADELE STREESEMAN, 64 121
- Your World and Mine By HALBERT L DUNN, 75 857
- $\beta$  Propylalbytylamine, (Notes) 76 1091-1096
- Brain, tuberculoma of, 62 654-666
- Breast, tuberculosis, 73 810-824
- Breathing *See also* Pulmonary function  
energy cost and control, in chronic pulmonary emphysema, 80 (Supplement, July 131)  
mechanics of  
gas exchange and pulmonary circulation, influence of ventilatory mechanics, 80 53-58  
physical properties of lung, 80 38-45  
respiratory work, 80 46-52  
positive pressure, intermittent  
in bronchopulmonary disease, 71 693-703  
in pulmonary emphysema, 76 33-46  
in pulmonary tuberculosis, 72 479-486
- Bronchial stenosis *See* Stenosis
- Bronchial tree, experimental exploration by tracheal fenestration, 78 815-821
- Bronchial tuberculosis *See* Tuberculosis
- Bronchial ulceration *See* Ulceration
- Bronchiectasis  
in ambulant clinic service, 66 157-176  
apical, tomography compared with bronchography, 74 348-399  
bronchography in, pre and postoperatively, 69 657-672  
cardiopulmonary function in, preoperative and postoperative, 69 671-711  
comparative study 67 29-41  
and pneumonia, acute 71 711-769

*Bronchiectasis cont*

- and postoperative lung function, 77 209-220
- prognosis, 66 157-176
- as related to bronchogenic carcinoma, 61 620-629
- and tuberculosis, relation between, 61 387-398
- Bronchioles, carcinoma arising from, 63 399-416
- Bronchitis
  - air pollution and, (editorials) 80 582-584
  - chronic, (Notes) 75 310-312
    - as etiologic factor in obstructive emphysema, 80 (Supplement, July 185-193)
    - physiologic defects in, 78 191-202
    - prevalence, nature, and pathogenesis of, 80 183-191
  - syndrome, and chronic emphysema, symposium on, Aspen (Colorado), June 13-15, 1958, 80 (Supplement, July 1-213)
  - tuberculous, in pulmonary resection, 61 185-192
- Bronchocavitory junction, effect of streptomycin on, in relation to cavity healing, 67 173-200
- Bronchodilation, in bronchopulmonary disease, 71 693-703
- Bronchogenic carcinoma *See* Tumors
- Bronchogenic tuberculosis *See* Tuberculosis
- Bronchograms, under hypnosis, (Notes) 79 525
- Bronchography
  - and angiopneumography, in tuberculous fibrothorax, 73 61-71
- † in bronchiectasis, pre- and postoperatively, 69 657-672
  - 3,5 dudo-4-pyridone N-acetic acid in, 74 178-187, 188-195, 77 32-38
    - effect on blood iodine, (Notes) 77 181-183
  - and histopathologic correlation, in tuberculosis, 73 681-689
  - in pulmonary tuberculosis, 64 394-407, 70 274-284
    - before surgery, 77 561-592
    - with iodized oil, 66 699-721
  - simplified, (Notes) 66 246-250
  - and tomography, in apical bronchiectasis, 74 388-399
  - with water soluble contrast medium, 68 760-770
- Broncholithiasis, 73 19-30
  - from histoplasmosis, (case reports) 77 162-167
- Bronchopulmonary disease
  - cytologic patterns in, 77 22-31
  - positive pressure and bronchodilation in, 71 693-703
- Bronchoscopy
  - bronchial perforation during, (case reports) 78 106-110
  - review of, 61 355-368
  - in tuberculosis, primary, of childhood, 74 (Supplement, August 267-278)
  - in tuberculous lesions, (Notes) 73 586-588
  - value of sputum examination after, (Notes) 77 716-718
- Bronchospirometry
  - complications after, (Notes) 66 244-245
  - investigations before and after resection and lobectomy for pulmonary tuberculosis, 75 710-723
  - study of pulmonary function after decortication, 66 509-521
  - during thoracic surgery, differential function in, 75 730-744
  - before and after thoracoplasty, 75 724-729
  - values, significance of, 75 699-709
  - vital capacity in, (Notes) 76 320-321
- Bronchostenosis, bilateral, tuberculous, in patient with normal roentgenographic findings, (case reports) 63 706-709
- Bronchus(1)
  - adenoma of 75 865-884
  - carcinoma of
    - with laryngeal carcinoma, (case reports) 74 438-440
    - and pneumonia, in adults, 76 47-63
    - and pulmonary tuberculosis, 73 853-867
    - in relation to calcified nodules in lung, 66 151-160
    - and silicosis, (case reports) 76 1088-1093
  - disease of
    - bronchographic-histopathologic correlation in, 73 681-689
    - in lungs resected for pulmonary tuberculosis, 68 657-677
  - endo-, hamartoma of, (case reports) 80 65-70
  - erosion, caused by calcified lymph node causing hemoptysis, (case reports) 65 206-209
  - major, complicated by secondary infection, carcinoma arising from, 63 255-274
  - minor, carcinoma arising from, 63 399-416
  - mucoid impaction, 76 970-982
  - papilloma of, (case reports) 78 916-920
  - papillomatosis of, (case reports) 71 429-436
  - perforation, during bronchoscopy, (case reports) 78 106-110
  - reconstruction, plastic, 64 477-488
  - regenerative versus atypical changes in, 79 591-596
  - resected, and postoperative complications, 74 874-884
  - supernumerary, and bronchial adenoma, (case reports) 75 326-330
  - tracheal, anomalous, to the right upper lobe, (case reports) 64 686-690

*Bronchus(s), cont*

- tuberculous
  - in dog, 73 748-763
  - lesions, intra- and extraluminal, 74 (Supplement, August 256-266)
  - "quiescent," 73 451-471

*Brucella abortus*

- infection in mice, 73 251-265
- in relation to *M. tuberculosis*, (correspondence) 74 478

*Brucella suis*, vaccines from gamma-irradiated, and from *M. tuberculosis*, (Notes) 79 374-377*Brucellosis*, human, caseation necrosis, (case reports) 67 859-868*Bulla(e)*

- emphysematous
  - complicated by hemorrhage and infection, surgical drainage of, (case reports) 61 742-746
  - infected, (case reports) 61 742-746, (case reports) 69 287-296
  - surgery, 74 856-873

**C**<sup>14</sup>C-labeled PAS-isoniazid, 75 71-82

## C-reactive protein, in pulmonary tuberculosis, (Notes) 74 464-467

## Calcification(s)

- intracranial, after tuberculous meningitis
  - in children, 78 38-61
  - serous, (case reports) 78 101-105
- pulmonary, disseminated, 62 1-16
  - scalene node biopsy in patients with, 72 91-97
  - and tuberculin, histoplasmin, and coccidioidin sensitivities in Rocky Mountain area, 59 643-649
- in pulmonary nodule, solitary, (case reports) 74 106-111
- of regional lymph nodes, following BCG vaccination, 73 239-245
- as related to bronchogenic carcinoma, 64 620-629

## tuberculous, renal, (case reports) 71 437-440

## Calcium benzoyl-PAS, (Notes) 75 667-669

## and calcium PAS, tolerability of, 79 351-356

Cancer *See also* Tumors and specific organs detected in tuberculosis surveys, 62 491-500

## of lung, 70 763-783

## cytologic diagnosis, 61 60-65

*Candida albicans* *See* FungiCaplan's syndrome *See* Pneumoconioses

## Carbohydrates, protein-bound, of blood serum in pulmonary tuberculosis, 75 793-806

## Carbolfuchsin, staining of mycobacteria in diagnostic films, 74 597-607

## Carbon dioxide narcosis, treated by resuscitator, 74 309-316

Carbon isotopes, in *M. tuberculosis*, 71 609-615

## Carbon monoxide diffusing capacity during exercise, 74 317-342

Carbovide<sup>®</sup> gas, for decontamination of articles made by tuberculous patients, 71 272-279Carcinoma *See* TumorsCardiac symptoms *See* Heart

## Cardiopulmonary disease, smoking in, 77 10-16

## Cardiopulmonary function

- in Boeck's sarcoid, cortisone in, 67 154-172
- in bronchiectasis, preoperative and postoperative, 69 869-914
- in chronic obstructive emphysema, 80 689-699
- in hematogenous pulmonary tuberculosis in patients receiving streptomycin, 64 583-601
- in pulmonary fibrosis, 80 700-704

## Cardiospasm, simulating mediastinal tumors, (case reports) 63 597-602

## Caseation necrosis, in brucellosis, (case reports) 67 859-868

Case finding *See also* Surveys

- in general hospitals, 70 304-311
  - and tuberculin test, (Notes) 79 378-381
- in general population, schools, and hospitals, 80 (Supplement, October 73-93)
- in psychiatric hospitals, resurvey interval of, (Notes) 79 537-540
- in tuberculosis, 71 406-418
- in Erie County (New York), 59 78-85
- by tuberculin testing, 78 667-681

Caseous pneumonic tuberculosis *See* Tuberculosis

## Cats in experimental tuberculosis, treated with isoniazid, 65 376-391

## Catalase

## activity

- correlated with isoniazid resistance and guinea pig virulence, (Notes) 72 246-251

## of isoniazid-resistant tubercle bacilli, (Notes) 69 471-472

of isoniazid-susceptible and -resistant strains of *M. tuberculosis*, (Notes) 79 669-671of *M. tuberculosis*, 78 735-748of *M. tuberculosis* H37Rv, (Notes) 80 257-258

## of tubercle bacilli, 76 1007-1015

## in bovine liver, inhibited by isoniazid, trace metals in, (Notes) 77 501-505

colorimetric test in *M. tuberculosis* cultures, (Notes) 71 305-307

## enzyme, of mycobacteria, 77 146-154

## in isoniazid resistance, 73 726-734

## peroxidase and isoniazid relation in mycobacteria, 75 62-70



- Cattle erythrocytes, PPD sensitization of, (Notes) 77 177-180
- Cavity (ies)
- coccidioidal, recurrent, after surgery, (case reports) 71 131-136
  - cystlike
    - in drug-tested rabbits, 75 965-974
    - in drug-treated tuberculosis, 77 221-231
    - in tuberculosis during isoniazid therapy, (Notes) 69 1054-1055
  - healing at bronchocavitary junction, streptomycin effect, 67 173-200
  - inspissated, prognosis, 59 53-67
  - in noninfectious patient, resection for, 74 169-177
  - nontuberculous, in experimental tuberculosis, produced by egg albumin, 75 99-104
  - "open negative," problem of, (ATS) 80 118-119
  - persistent, and noninfectious sputum
    - during chemotherapy, and relationship to "open healing," 75 242-258
    - home care in, 77 764-777
  - pulmonary
    - in anthracosis, 71 544-555
    - in development of streptomycin resistance, 59 391-401
    - from *Histoplasma capsulatum*, (case reports) 69 111-115
    - in lower lobe, 63 625-643
    - roentgenographic simulation of, 71 529-543
    - tension, (correspondence) 77 368
      - pathogenesis and treatment, 76 370-387
    - in tuberculosis, chemotherapy and phenomenon of open cavity healing, (editorials) 71 441-446
  - tuberculous
    - gaseous content, 80 1-5
    - giant
      - healing, (Notes) 78 140-144
      - surgery, 77 593-607
    - "open-healing," 72 601-612, 75 223-241, 242-258
      - under chemotherapy, (case reports) 73 944
    - in resected specimens, 72 158-170
- Cell(s)
- alveolar, carcinoma, 79 502-511
  - cultures, mycobacteria in, 77 789-801
  - HeLa
    - atypical mycobacteria in, 77 968-975
    - growth characteristics of acid-fast microorganisms other than tubercle bacilli in, (Notes) 80 744-746
    - M. tuberculosis* in, 77 423-435
  - lysis, in tuberculin sensitivity, 68 746-759
  - mammalian, and mycobacteria in tissue culture, (correspondence) 75 347-348
  - mycobacterial, crude, biologic activity of, (Notes) 80 274-276
  - sonic-treated, in transfer of tuberculin hypersensitivity, 73 246-250
  - tuberculin sensitized, inhibition of, *in vitro*, 80 410-414
- Centrifugation, for concentrating tubercle bacilli, (Notes) 76 899-901
- Cerebellopontine angle, tuberculoma of, simulating acoustic neuroma, (case reports) 63 227-229
- Cerebral vessels, thrombosis of, with necrosis of the basal nuclei, 61 247-256
- Cerebrospinal fluid, in tuberculous meningitis, transfer of glucose into, 67 732-754
- Charcoal
- diluents, for tubercle bacilli, 70 989-994
  - medium
    - for tubercle bacilli, 70 955-976, 71 382-389
    - drug susceptibilities, (Notes) 71 447-451
- Chemoprophylaxis
- in chronic obstructive pulmonary emphysema, 80 716-723
  - and inhibition of immunity, 74 541-551
  - with isoniazid, in experimental tuberculosis, (correspondence) 74 475-476
  - in tuberculosis, (editorials) 74 117-120, 80 648-658 (Supplement, October 1-21)
- Chemotherapy *See also* Antimicrobials, Drugs, and specific drugs
- of actinomycosis, 63 441-448
  - antituberculosis, dynamics of, 74 (Supplement, August 100-108)
  - in conjunction with surgery, (correspondence) 74 476-478
  - cross-resistance of *M. ranae*, 69 267-279
  - effectiveness, shown by use of guinea pig omentum, 68 583-593
  - healing process, 79 497-501
    - natural, (editorials) 76 669-670
    - of tuberculous open cavity, (case reports) 73 944-955
  - in histoplasmosis, 75 912-920
  - of leprosy, evaluation of drugs, 69 173-191
  - of miliary and meningeal tuberculosis in the adult, 69 912-925
  - of nocardiosis, 63 441-448
  - original, of noncavitary pulmonary tuberculosis, isoniazid and isoniazid-PAS in, 80 641-647
  - of photochromogenic mycobacterial infections, 80 522-534
  - in pneumoconiosis, complicated by tuberculosis, (correspondence) 79 818
  - and pneumotherapy, antagonistic effect, (correspondence) 70 533-537, (correspondence) 71 600-602, 766

*Clofazimine*

- prolonged causing drug resistance of tubercle bacilli, (Notes) 76 871-876
- relapse of tuberculous lesions during and after, 80 (Supplement, October 17-71)
- resistance of tubercle bacilli to drugs, 61 385-507
- and tuberculin sensitivity in rabbits, 70 329-335
- of tuberculosis, 61 107-121, 70 192-196
- active, (correspondence) 63 190-192
- cycloserine-isoniazid in, (Notes) 60 89-91
- arrested in guinea pigs by reinfection, 80 551-558
- clinical and histopathologic study of, 69 217-220
- with Conteben<sup>®</sup>, 61 20-38
- experimental, 60 223-227, 61 541-550
- heterocyclic acid hydrazide and derivative 67 367-375
- isoniazid and derivatives, 67 351-365, 68 111-115
- in mice, 69 104-110
- action of streptomycin PAS in, (correspondence) 60 808-810
- intrapertoneal infection in screening of drugs 69 289-296
- hospital and home in, 80 (Supplement, October 23-45)
- in infants and children, 71 (Supplement, August 225-231)
- intestinal, as prophylaxis, 61 130-141
- long term, and prognosis, (correspondence) 70 178
- primary
  - in children, 69 682-689
  - segmental lesions in, 756-763
  - and prognosis, (correspondence) 70 335-536
- pulmonary
  - and ambulation, 70 1030-1041, (correspondence) 71 602-603
  - effect on healing rate, 76 988-1001
  - fibrocascous, chronic, relapse rates after, (Notes) 71 302-304
  - isoniazid with PAS-pyridoxine, (Notes) 78 773-784
  - lesions after, 71 165-185
  - phenomenon of open cavity healing, (editorials) 71 111-116
  - prolonged indefinitely, 70 219-227
  - relationship to surgery, 80 (Supplement, October 95-115)
  - roentgenographic spread, during sanatorium residence before, 68 863-873
  - streptomycin plus isoniazid-PAS-pyridoxine, 78 779-784

- renal, urine cultures during, 70 149-154
- sulfones in the mouse, 63 556-567
- of tuberculous meningitis, 69 192-201
- in children, 76 832-851
- of tuberculous patients
  - nonhospitalized, 70 1012-1053, 75 11-52
  - noninfectious, to prevent relapse, (correspondence) 80 108
- viability of tubercle bacilli with and without, (Notes) 67 871-877

## Chest

- examination, acoustic basis, 72 12-34
- lesion
  - asymptomatic and circumscribed, 62 512-517
  - undetected in mass surveys, 61 249-255
- roentgenograms
  - in Baroness Erlanger Hospital (Chattanooga, Tennessee), 60 377-382
  - interpretation of, 61 225-248
- surgery *See* Surgery, Thoracoplasty
- survey *See* Roentgenography
- taping, 76 167-172
- wall
  - spontaneous abscesses, 62 (Supplement, July 18-67)
  - tuberculous sinuses, 66 732-743

## Chick embryo(s)

- extract, failure to accelerate growth of tubercle bacilli, (Notes) 65 783-785
- mycobacteria in, 73 276-290
- and *M. tuberculosis*
  - virulence, 71 219-257
- yolk sac method for isolating, (Notes) 77 511-515

Children *See also* Infants

- antihistamine medication on tuberculin reaction in, 60 354-358
- school-age, Liberian, tuberculin patch-test survey among, (Notes) 67 665-668
- tuberculin tests in, 60 45-50
- tuberculosis in, 74 (Supplement, August 1-6)
  - hemagglutination reaction, 70 139-148
  - miliary and meningeal, streptomycin-promizole<sup>®</sup> therapy for, 61 159-170
- primary
  - chemotherapy, 69 682-689, 79 756-763
  - value of follow-up studies, 64 499-507
  - streptomycin-resistant tubercle bacilli in, 66 63-76
- of tuberculous patients, risk of developing tuberculosis among, 70 1009-1019

## China, chest survey, 72 356-366

## Chlortetracycline

- antituberculous activity of, 72 367-372
- in pulmonary tuberculosis, 59 624-631, 61 875-880

*Chlortetracycline cont*

- tuberculostatic activity *in vitro* and *in vivo*, (correspondence) 59 221, 60 143
- Cholecystitis, tuberculous, (case reports) 70 731-738
- Choleraesuis infestation, with cystic disease, (case reports) 71 92-98
- Chromogens, acid-fast, in gastric juice of non-tuberculous patients, (correspondence) 79 543-544
- Circulation
  - dynamics in pulmonary emphysema, during exercise, 80 (Supplement, July 128)
  - pulmonary
    - arterial, effects of alteration, on tuberculosis in monkeys, 65 48-63
    - capillary, 71 822-829
- Cirrhosis, cardiac, with obscure pulmonary arteriosclerosis and right heart failure (Ajerza's disease), (case reports) 70 1083-1091
- Cleavage, metabolic, of antituberculous thioethyl compounds, 74 78-83
- Clinic, chest, hemoptysis in patients of, 63 194-201
- Coal miners *See* Pneumococcosis, anthracite
- Coccidioidal cavity *See* Mycoses
- Coccidioidal granuloma *See* Mycoses and Tumors
- Coccidioides immitis* *See* Fungi
- Coccidioidin *See* Fungal antigens
- Coccidioidomycosis *See* Mycoses
- Coenzymes I and II *See* Pyridine nucleotides
- "Coin lesions"
  - simulated by fibrin bodies, (case reports) 72 659-662
  - of lung, (Notes) 73 134-138
- Collagen, of lung, 80 (Supplement, July 45-48)
- Collapse
  - pulmonary, electrocardiographic changes after, 64 50-63
  - therapy, in tuberculous psychotic patients, 67 232-246
- Collodion agglutination *See* Agglutination
- Colorado, Aspen
  - "first" conference, postscript to, 80 (Supplement, July 213)
  - Symposium on Emphysema and the "Chronic Bronchitis" Syndrome (June 13-15, 1958), 80 (Supplement, July 1-213)
- Communicability of histoplasmosis, 63 538-546
- Compounds, antituberculosis, chemotherapeutic decomposition, (Notes) 73 593-596
- Concentration agents, lethal action on tubercle bacilli in sputum, 69 991-1001
- Contagiousness of coccidioidomycosis, 61 95-115
- Conteben® *See* Thiosemicarbazones
- Cor pulmonale
  - polycythemia, and idiopathic hypoventilation, (case reports) 80 575-581
  - after resection, 77 387-399
- "Cord factor"
  - relation to pathogenicity, 77 482-491
  - of tubercle bacillus
    - isolated from petroleum ether extracts of young bacterial cultures, 67 629-643
    - occurrence in chloroform extracts of young and older bacterial cultures, 67 828-852
    - occurrence in various bacterial extracts, 67 853-858
    - toxicity of, mechanism, 80 240-248
- Cord formation
  - relation to virulence, 78 83-92
  - titration, in acid-fast, wild-type, typical and atypical bacilli, (Notes) 78 799-801
- Cornea, tuberculosis, cortisone in, study with phase-contrast microscope, 74 1-6
- Coronary artery *See* Artery
- Coronary disease *See* Heart
- CORRESPONDENCE
  - absorption of shellac-coated PAS granules, with special reference to the age of the preparations, 76 159
  - acid-fast bacilli, nonpathogenic for guinea pigs, 74 478-480
  - acid-fast chromogens, frequency of, in gastric juice of nontuberculous patients, 79 543-544
  - aliphatic amines, effect on ability of virulent mycobacteria to bind neutral red, 60 384
  - allergy
    - exacerbation of pulmonary tuberculosis, 74 155-157
    - lethal allergic shock in experimental tuberculosis under streptomycin therapy, 75 343-344
  - ambulation of tuberculous patients under protection of chemotherapy, 71 602-603
  - antimicrobial therapy
    - in primary tuberculous infection in children, 72 398-402, 73 305
    - and prognosis of primary tuberculosis, 70 535
- BCG
  - fatal case of tuberculosis produced by, 71 321-323, 73 301-305
  - method of obtaining, 79 105
  - standardization, 65 641
  - Tice stain, 75 692-693

*Conferences, ECG, etc.*

- vaccination 62 116-119
  - hyaluronidase effect on, 65 217-218
  - in Sweden, 70 678-679
- beryllium case registry at Massachusetts General Hospital, 72 129-132
- carbohydrate antilodies, precipitin test for, 59 710-712
- cure of tuberculosis in countries of limited means 73 444-445
- chemotherapeutic activity
  - of streptomycin-PAS in experimental tuberculosis in mice, 63 808-810
  - of Triton WR 1339-macrocyclon in murine leprosy, 76 913-916
- chemotherapy
  - for all active tuberculosis, 63 490-492
  - with eventual surgery in mind, for tuberculous patients, 71 476-478
  - in pneumoconiosis complicated by tuberculosis, 70 818
  - possibility of an antagonistic effect between pneumothorax and, 70 333, 71 600-602, 766
  - to prevent relapse in patients with noninfectious tuberculosis, 80 108
  - prognosis of long term, in tuberculosis, 70 178
- chlorotetracycline in tuberculostatic activity, 70 221, 60 113
- chromogenic acid fast bacilli from human sources, 72 603-604, 73 601-603
- coccidioidomycosis
  - contagiousness, 61 141
  - pulmonary, 61 158
- comminution of mycobacteria by exposure to ultrasonics, 76 911-915
- concerning apical localization of postprimary pulmonary tuberculosis explained by the specific gravity of tuberculous material, 73 598-600
- DIAGNOSTIC STANDARDS—1950 edition, 63 721-722
- DIAGNOSTIC STANDARDS AND CLASSIFICATION OF TUBERCULOSIS, 1950, 74 158-159
- differential response to metabolites of *M. tuberculosis* H37Rv and H37Ra, 62 333
- diffuse interstitial pulmonary fibrosis and hypertrophic pulmonary osteoarthropathy, 79 513
- discharges from hospital, irregular, terminology for, 68 631-635, 73 597
  - fate of tuberculous patient and, 72 552-554
  - from tuberculosis sanatoriums, 70 755
  - in the U S A and Great Britain, 69 847-851
- effect of antihistamine medication on the tuberculin reaction, 60 811, 61 442
- effect of iodine on tuberculosis, 66 765-777
- enzymatic characteristics of suspensions of different mycobacteria, 61 270-271
- establishment of a beryllium case registry, 67 911-912
- filterable forms of *M. tuberculosis*, 69 473-474
- genitourinary transmission of tuberculosis, 75 153-155
- globulin titration technique, false positive reactions in, as applied to tuberculosis, 76 507-508
- hand talking chart, 70 531-535
- historic collection of pneumothorax machines and needles, 80 278
- importance of the social sciences for the control of tuberculosis in underdeveloped areas of the world, 75 345-346
- incidence of tuberculous infection in infancy, 71 808-809
- International Union Against Tuberculosis, 78 810
- iodine in leprosy, 68 295-296
- isoniazid
  - bacteriostatic action of, in presence of PABA, 76 706-707
  - chemoprophylaxis, in experimental tuberculosis, 74 475-476
  - clinical evaluation, 70 1102-1103
  - and coccidioidomycosis, pulmonary, 61 158
  - delirium, 69 845-846
  - diabetes affected by, 67 544
  - further observations on the correlation between serum concentrations and therapeutic response in human pulmonary tuberculosis, 80 108-110
  - indications for antituberculosis prophylaxis in the course of nontuberculous disease, 78 485
  - and mechanism of increasing bacteriotropic potencies of, in presence of PABA, 78 949-951
  - mode of action, 75 517-518
  - possible immediate deleterious effect on course of tuberculous meningitis, 71 765, 74 480
  - proposed mechanism of action for, in the tubercle bacillus and other biologic systems, 69 1062-1063
  - toxicity, 68 296-297
    - for the monkey, 68 470
  - used alone in the treatment of pulmonary tuberculosis, 70 924-925
- isoniazid C<sup>14</sup>, differential uptake by *M. paratuberculosis* susceptible and resistant to isoniazid-hydrogen peroxide, 80 110-111
- limitations of the guinea pig test, 70 374-375

*Correspondence, isoniazid, cont*

lung immobilizer therapy in pulmonary tuberculosis, 67 267

"mass X-ray" surveys, 60 532-535

mechanism of exacerbation in pulmonary tuberculosis with special reference to allergy, 74 155-157

mycobacteria, virulent

modified microcolonial test for, 73 600-601

in vitro, oxidation-reduction dyes for the determination of, 66 382-383

*M. tuberculosis*

possibility of sexual cycle, 63 721

relationship between *B. abortus* and, 74 478

*M. tuberculosis* H37Rv, 77 1031-1032

nucleinemia, 67 545-546

pancreas vs omentum in experimental tuberculosis, 80 445

pathogenesis and treatment of pulmonary tension cavities, 77 368

perils of procrastination in phthisiotherapy  
urgent indications for antituberculosis medication, 74 153-155

personnel pressure and the tuberculous patient, 76 912-914

plea for clearer distinction between allergic granulomatosis and Wegener's granulomatosis, 79 544-545

(on) Pinner's book, *Autobiographical Sketches of Disease by Physicians*, 63 492

pneumothorax induction, 69 844-845, 70 755

artificial, 72 252, 694

methods, 70 373-374

traumatic, 70 536-537

problem of the so-called "good chronic" case of tuberculosis, 66 381

problems in laboratory diagnosis of tuberculosis, 76 1110-1111

proper designation of ammonium sulfate PPD, 74 810-811

proposal for reducing cost of care of the tuberculous in countries of limited means, 73 444-445

psychiatric evaluation of the personality of the tuberculous patient, 74 807

pulmonary tuberculosis during long-term single-drug (isoniazid) therapy, 71 314-315

rehabilitation and occupational therapy in tuberculosis hospitals, 79 680, 80 445-447

rehabilitation of tuberculous patients, 80 111-112

relationship of mycobacteria and mammalian cells in tissue cultures, 75 347-348

request for data on effects of cortisone and ACTH on tuberculosis in humans, 64 471-472

request for reprints concerning stress and the adaptive hormones, 67 677-678

resistance of a tuberculin reactor, 69 846-847

sarcoidosis, 75 852-854

failure to develop, after oral ingestion of pine pollen, 80 760

finding of lupus erythematosus cells in, 74 811

sensitivity to histoplasmin, 61 269

serum gamma-globulins in pulmonary tuberculosis, 61 893-894

sophistry in use of the word "minimal," 79 681

source of scotochromogens, 80 277-278

sputum collection during local anesthesia, 75 854-855

"sputum conversion" and the metabolism of isoniazid, 77 869-871

streptomycin-isoniazid resistance, 75 346-347

surgical vs nonsurgical treatment of "open-negative" syndrome, 76 508-509

surgical reporting, 79 679-680

survival of bacilli in tuberculous lesions, 66 381-382

technique of drug-resistance tests, 70 922-923

terminology used for discharges from hospital, 80 447-448

test for PAS ingestion, 74 810

torsion of the spleen associated with pneumoperitoneum, 70 923

treatment

of active pulmonary tuberculosis outside institution, 76 506-507

failures, 79 105

of a recent tuberculin reactor, 69 843-844

of tuberculous lymphadenitis with sodium salicylate, 68 940-941

tubercle bacilli

counting chambers for enumeration of, 70 376-377

culture of, in test tubes or bottles, 77 1030

growth of, in monocytes from normal and vaccinated rabbits, 69 1059-1060

growth requirements

isoniazid-resistant, 75 155-156

virulence of, 69 640-641, 70 370-372

isolation, rapid microculture method for, 76 159-160

methanol extracts, 74 807-808

procedure for negative cultures of, 68 470-471, 69 128

simple device for microculture in blood, in pathologic specimens, 73 785-786

streptomycin-resistant, transmission of, 62 227

treated with isoniazid, virulence of, 69 641-644

viable and stainable counts, in tuberculous tissue, 75 519-520

- of tubercle bacilli, diagnostic media for, 63 159-169, 170-175  
 Cyanacetic acid hydrazide, antituberculosis value of, 71 117-127  
 Cyclo crime  
   alone and in combination with other drugs in experimental tuberculosis, (Notes) 75 510-513  
   antituberculosis activity *in vitro* and *in vivo*, 73 539-546  
   ATS statement by Committee on Therapy, 75 1016-1017  
   clinical, bacteriologic, and pharmacologic observations on, (Notes) 71 128-135  
   disposition in humans, 71 739-746  
   effect on tubercle bacilli, 72 685-686  
   in experimental animals, (Notes) 71 802-806  
   -ironazid  
     in ambulant tuberculosis therapy, (Notes) 80 89-94  
     in tuberculosis, pulmonary, (Notes) 79 87-88  
     high dosage, (Notes) 80 269-273  
     with other drugs, 75 553-576  
   -pyriminide, in pulmonary tuberculosis, (Notes) 78 927-931  
   toxicity, 71 196-209, (Notes) 75 511-516  
   and pharmacology, (Notes) 71 972-976  
   in tuberculosis  
     experimental, (Notes) 72 117, 856-858  
     human, (Notes) 71 121-127  
     pulmonary, (Notes) 76 1097-1099  
     psychologic effects, (Notes) 73 438-441  
   -viomycin, in pulmonary tuberculosis, (Notes) 79 90-93  
   *in vitro* action on *M. tuberculosis*, (Notes) 72 236-241  
 Cystic disease, bronchogenic, with choleraesuis and *Aspergillus* infestation, (case reports) 71 92-98  
 Cystoscopes, sterilization, (Notes) 76 909-911  
 Cyst(s)  
   intrathoracic, after oleothorax, (case reports) 66 601-604  
   of lung See Cysts, pulmonary  
   primary mediastinal, and neoplasms in children, 71 910-953  
   pulmonary, 75 53-61  
     infected by *M. tuberculosis*, (case reports) 69 1037-1041  
     surgical management of, (case reports) 63 579-586  
   vascular anomalies associated with, (case reports) 71 573-583  
 Cytology, in diagnosis of pulmonary malignancy, 61 60-65

- Cytolysis test, of leukocytes  
 "plasma factor" in, (Notes) 79 244-245  
*in vitro*  
 in sarcoidosis, 63 672-673  
 by tuberculin, 60 212-222
- Cytotoxicity of tuberculin, *in vitro*, failure to demonstrate for the cells of sensitized animals, 63 674-678
- D**
- Deborah Sanatorium and Hospital (Philadelphia, Pennsylvania), international symposium, November 20-22, 1958, 80 (Supplement, October 1-139)
- Decontamination of articles made by tuberculous patients, Carboxide® gas for, 72 272-279
- Decortication of lung  
 pulmonary function after, 63 231-251  
 bronchspirometric study, 66 509-521  
 in pulmonary tuberculosis, 59 30-38, 60 288-304
- Deformities, prevention of, after thoracoplasty, 66 436-448
- Desoxyribonucleic acid  
 failure to induce bacterial transformation, (Notes) 80 911  
 as growth stimulant of tubercle bacilli, 80 866-870
- Detention ward, in tuberculosis treatment and control, 74 410-416
- Diabetes  
 alloxan-induced, in albino rats, 65 603-611  
 insipidus, pulmonary histiocytosis with, (case reports) 79 652-658  
 isoniazid effect on, (correspondence) 67 544  
 and tuberculosis, 65 (Supplement, January 1-50), 76 1016-1030, 77 990-998  
 surgery for, 74 747-755
- Diagnosis  
 by auscultation, 60 639-647  
 bacteriologic, 59 589-598  
 differential  
 bronchogenic carcinoma as a problem of, in pulmonary disease, 63 176-193  
 of pulmonary lesions, importance of tuberculin test in, 63 140-149  
 of pulmonary tuberculosis, tracheal lavage and culture in, 60 634-638
- DIAGNOSTIC STANDARDS AND CLASSIFICATION OF TUBERCULOSIS of the National Tuberculosis Association  
 1950 edition, (correspondence) 63 721-722  
 history of, 65 494
- 4 4'-Diaminodiphenyl sulfone, excretion products, (Notes) 72 123-125
- Diaphragm  
 pneumocele in, complicating therapeutic pneumoperitoneum, 69 745-759  
 rupture of  
 complicating pneumoperitoneum, resulting in spontaneous pneumothorax, (case reports) 63 587-590  
 during pneumoperitoneum, (case reports) 60 794-800
- Diatomaceous earth, pneumoconiosis and, 77 644-661
- Diet(s)  
 controlled, urinary excretion in, 69 439-454  
 effect on resistance by viable and nonviable vaccines, 77 93-105
- Differential diagnosis *See* Diagnosis
- Diffusing capacity for oxygen during exercise, 80 806-824
- Dihydrostreptomycin  
 in avian tuberculosis in chicks, comparison with streptomycin, 60 366-376  
 -corticotropin, in experimental bovine tuberculosis in rabbit, 67 201-211  
 -cortisone, in experimental tuberculosis in guinea pig, (Notes) 67 101-102  
 neurotoxicity, effects of longer-term therapy, 63 312-324  
 -PAS, in experimental tuberculosis in guinea pigs, 62 149-155  
 purified, (Notes) 73 776-778  
 resistance, genetic studies of, in *M. ranae*, 62 286-299  
 sulfate, in pulmonary tuberculosis, neurotoxicity of, 65 612-616  
 toxicity, 60 564-575  
 -Triton A-20 in experimental tuberculosis in mice, 65 718-721  
 tubercle bacilli, dihydrostreptomycin-resistant strains, enhancement of growth by, a function of initial pH value of the medium, 63 568-578
- in tuberculosis  
 experimental, in guinea pigs, effect of in combination with Tibione® as compared when combined with PAS, 63 339-345  
 pulmonary, 62 572-581  
 compared with streptomycin, 68 229-237, 238-248  
 in tuberculous empyema, drug concentrations attained with various vehicles, 66 271-284  
 cellugel as vehicle, 66 285-291
- 3,5-Diiodo-4-pyridone N-acetic acid in bronchography, 74 178-187, 188-195, 77 32-38  
 effect on blood iodine, (Notes) 77 181-183

- 1,4-Dimethyl-8-isopropyl-bicyclo-decapentane-Triton A-20, therapeutic activity in experimental tuberculosis and leprosy, (Notes) 75 684-687
- Dionosil® See 3,5-Duodo-4-pyridone N-acetic acid
- Discharge(s) (from hospital)
- irregular, of tuberculous patients, 66 213-216, 68 393-399, (correspondence) 69 634-635, (correspondence) 70 755, 71 419-428, (correspondence) 72 552-554, (correspondence) 73 597
  - problem of, (editorials) 70 892-898
  - scale for predicting, 73 338-350
  - special ward procedure, 72 633-646
  - in the U S A and Great Britain, (correspondence) 69 847-851
  - terminology, (correspondence) 80 447-449
- Discriminant analysis, in prediction of relapse in pulmonary tuberculosis, 73 472-484
- Disease, chronic, time factor in studies of the outcome, (editorials) 63 608-612
- Dispersion, in relation to virulence of tubercle bacilli, 75 488-494
- Dissemination of tubercle bacilli in experimental tuberculosis in guinea pigs, 61 399-406
- Diverticula, traction, of esophagus in middle lobe syndrome, 65 455-464
- DL-Serine, toxic effects on virulent human tubercle bacilli, (correspondence) 60 385
- Dogs, amithiozone toxicity in, 64 659-668
- isoniazid-isoniazid effect on central nervous system in, 69 261-266
- tuberculosis in
- bronchogenic, 73 748-763
  - experimental, 61 77-94
  - treated with isoniazid, 65 376-391, 392-401
- Douglas bag, in maximal breathing capacity with spirometry, (Notes) 79 253-255
- Drainage
- closed, and thoracoplasty in tuberculous empyema, 66 522-533
  - following pulmonary resection, (Notes) 69 636-637
  - lymphatic, of pleural space in dogs studied with radioactive gold (AU<sup>198</sup>), (Notes) 75 145-147
  - surgical, of emphysematous bulla, (case reports) 61 742-746
- Drug(s) See also Antimicrobials, Chemotherapy, and specific drugs
- ancillary, in resection of drug-resistant cavitary tuberculosis, 79 780-789
  - antituberculosis
  - roentgenography as index of effect of, 68 65-74
  - screening of, in guinea pigs, 68 48-64
  - therapy with paired combinations of, 80 627-640
  - in tuberculosis, (Notes) 78 121-126
  - fever, due to isoniazid, (case reports) 68 249-252
  - new, in tuberculosis, scientific appraisal of, (editorials) 61 751-756
  - resistance
  - in pulmonary resections, 75 781-792
  - tests (correspondence), 70 922-923
  - susceptibility tests, *in vitro*, with *M. tuberculosis*, 63 679-693
  - therapy
  - preresection, in pulmonary tuberculosis, 79 41-46
  - in tuberculosis, (Notes) 74 968-971
- Dubos medium See Medium(a)
- Dubos-Middlebrook hemagglutination test See Hemagglutination
- Duck embryos, mycobacteria in, 73 276-290
- Duodenum, rupture, with arteritis of abdominal aorta, (case reports) 60 801-807
- Dusts See also Pneumoconioses
- Fiberglas®-plastic, and tuberculosis, 78 512-523
- Dyes, oxidation-reduction, in determination of virulence of mycobacteria *in vitro*, 65 187-193
- Dyspnea
- in beryllium workers, 59 364-390
  - in Parkinson's syndrome, 78 682-691
- E**
- Eating utensils, tuberculous contamination of, (Notes) 74 462-463
- EDITORIALS**
- air pollution and bronchitis, 80 582-584
  - antihistamines and the tuberculin reaction, 62 555
  - acceleration of tuberculosis research, 71 140-143
  - BCG vaccine
  - immunologic aspects, 60 670-674
  - progress toward standardization of, 79 80-82
  - changes ahead for the American Trudeau Society, 75 648-649
  - chemoprophylaxis, immunity, and prevention in tuberculosis, 74 117-120
  - closing of the Trudeau Sanatorium, 71 163-164
  - cooperative clinical research in tuberculosis, 68 263
  - cost of tuberculosis research, 60 527-531
  - creative spirit in research, 64 113-116
  - effect of isoniazid on the program of the tuberculosis association, 66 615-620
  - emotional problems in the treatment of tuberculosis, 71 299-301



*Editorials, cont*

- fiftieth anniversary of the National Tuberculosis Association, 69 631-633
- hemagglutination test in tuberculosis, 62 223-226
- on history repeating itself, 74 793-795
- implications of the phenomenon of "open cavity" healing for the chemotherapy of pulmonary tuberculosis, 71 441-446
- implications of rapidly effective tuberculosis therapy, 61 892
- integration of streptomycin with other forms of therapy for pulmonary tuberculosis, 50 264-268
- limitations of knowledge about para-aminosalicylic acid, 76 491-496
- lymph node tuberculosis and its treatment in accessible nodes, 64 691-694
- mass roentgenographic surveys in small hospitals, 64 313-317
- natural healing and chemotherapy, 76 669-670
- natural history of tuberculosis in the human body, 80 100-107
- necessity for accurate evaluation of the results of thoracoplasty, 60 383
- philosophy of abstracting, 62 446-448
- place of the laboratory in the tuberculosis sanatorium, 73 291-293
- pneumothorax induction by lung puncture or "orthodox" technique, 69 121-124
- problems
  - of immunity in nontuberculous infections, 71 592-595
  - of irregular discharge, 70 892-898
  - of tuberculosis in psychotics, 68 782-785
- psychologic aspects of tuberculosis, 67 869-873
- relationship(s)
  - of the immunity mechanism to pathologic changes, clinical symptoms, and therapeutic measures in tuberculosis, 68 933-937
  - of tuberculous infection to illness, 71 885-888
- scientific appraisal of new drugs in tuberculosis, 61 751-756
- share in the task ahead, 67 517-521
- specific therapy for tuberculous meningitis, 61 263-268
- specificity of the tuberculin reaction, 63 355-359
- standardization and stability of purified tuberculin, 80 255-256
- thirty years of tuberculosis therapy in a municipal sanatorium, 70 518-520
- time factor in studies of the outcome of chronic disease, 63 608-612
- treatment
  - of female genital tuberculosis, 75 501-505
  - by inhalation, 74 454-456
  - tuberculosis
    - as a cause of female sterility, 70 1096-1098
    - in medical teaching, 60 140-142
    - on the Navajo reservation, 61 586-591
  - tuberculous alcoholic before and during hospitalization, 79 659-662
  - vocational rehabilitation in pulmonary tuberculosis today, 78 647-649
  - United States Public Health Service cooperative clinical investigation of bacterial resistance, 70 739-742
  - World Health Organization and tuberculosis, aims, objects, and accomplishments, 64 218-222
  - understanding of personality patterns as guide for rehabilitation of the tuberculous, 65 481-483
- Education for tuberculous patients, 70 490-497
- Effusion(s)
  - peritoneal, complicating pneumoperitoneum, (case reports) 66 90-94
- pleural
  - biopsy, 78 8-16
  - idiopathic, 72 647-652
  - thoracotomy in, 74 954-957
- pathology, 71 473-502
- primary, 59 259-269
- serofibrinous, in military personnel, 71 616-634
- proteins and mucoproteins, 76 247-255
- tuberculous, 62 314-323
  - age distribution of, (Notes) 70 901-902
  - in children, 77 271-289
  - modified bed rest in, 67 421-431
  - prednisone in, 79 307-314
- Egg(s)
  - albumin, in production of nontuberculous cavities in experimental tuberculosis, 75 99-104
- embryo
  - in rapid detection of tubercle bacillus, (Notes) 76 315-320
  - isolation of *M tuberculosis* on, (Notes) 70 912-915
- yolk media
  - in isolation of *M tuberculosis*, (Notes) 72 863-865
  - for tubercle bacilli, 70 977-988
- Elastin, of lung, 80 (Supplement, July 45-48)
- Electrocardiography
  - changes in
    - after chest surgery, 59 128-139
    - after mediastinal shift, 64 64-70
    - after pulmonary collapse and surgery, 64 50-63
  - in pneumoperitoneum, 61 335-345
  - with prominent S waves, 62 307-313
  - in pulmonary tuberculosis, surgically treated, 65 443-450

- Electro encephalogram, isoniazid effect on, 70 176-182
- Electron microscopy *See* Microscopy
- Electrophoresis
- effect of cortisone, and the hemagglutination reaction in childhood tuberculosis, 73 964-965
  - in study of serum proteins in tuberculosis, 68 372-381, (Notes) 75 999-1002, (Notes) 76 892-895, (Notes) 79 522-524
  - zone, in starch gels, report on Smithies method in normal adults and in patients with tuberculosis, 78 932-933
- Embolism
- air
    - in pneumoperitoneum, 69 396-405
    - mitral murmur presumably caused by, (case reports) 70 1092-1095
- Embolus, experimental, localization of, 70 557-569
- Embryo, chick, efficacy as medium for isolating tubercle bacilli, (Notes) 76 703-705
- Emotions of tuberculous patients, effect of isoniazid on, 68 523-531, 70 476-482
- Emphysema
- air-flow physics in, 80 (Supplement, July 123-125)
  - allergy in, 80 (Supplement, July 181-183)
  - alveolar, chronic, in horse ("heaves"), 80 (Supplement, July 141-143)
  - bullous
    - bilateral, pulmonary function tests in, (case reports) 71 867-876
    - after resection, 77 387-399
  - and "chronic bronchitis" syndrome, symposium on (Aspen, Colorado, June 13-15, 1958), 80 (Supplement, July 1-213)
  - clinical aspects, 80 (Supplement, July 169-171)
  - conference, summary of, 80 (Supplement, July 209-212)
  - definition, 80 (Supplement, July 114)
  - diagnosis, physical and roentgenographic signs and oximeter test in, 80 705-715
  - diffuse, obstructive, surgery in, 80 825-832
  - experimental
    - in guinea pig, 80 (Supplement, July 147-151, 153-154)
  - familial, 80 (Supplement, July 179-180)
  - longitudinal studies in, (Notes) 80 915-918
  - macrosection and injection studies of, 80 (Supplement, July 94-103)
  - in man, natural history of, 80 (Supplement, July 169-171)
  - mediastinal
    - complicating pneumoperitoneum induction, (case reports) 63 591-596, 68 775-781
    - therapeutic, (Notes) 76 897-898
  - spontaneous, and bilateral spontaneous pneumothoraces, 61 883-886
  - microradiography, 80 (Supplement, July 104-112)
  - obstructive
    - chronic, cardiopulmonary function in, 80 689-699
    - chronic bronchitis as etiologic factor, 80 (Supplement, July 185-193)
    - corticotropin-cortisone in, 64 279-294
    - pathogenesis, theories of, 80 (Supplement, July 2-4)
  - pathology, 80 (Supplement, July 58-64)
  - pulmonary
    - chronic, 69 915-929
      - basic lesion in, 68 24-30
      - breathing, energy cost and control of, 80 (Supplement, July 131)
      - pathogenesis, 62 45-57
      - respirators in, 80 510-521
      - ventilation in, 74 210-219, 220-228
    - circulatory dynamics, during treadmill exercise, 80 (Supplement, July 128)
    - in coal miners, 59 270-288
    - diffusion in, 71 249-259
    - early, 72 569-576
    - experimental, 78 848-861, 80 (Supplement, July 158-167)
    - hypoxia due to, hematologic adaptation in, 78 391-398
    - lymphatics in reference to, 80 (Supplement, July 50-56)
    - obstructive, chronic
      - chemoprophylaxis in, 80 716-723
      - cigarette effects in, 76 22-32
    - and peptic ulcer, 80 (Supplement, July 155-156)
    - severe, intermittent positive pressure breathing in, 76 33-46
    - surgery in, 80 (Supplement, July 194-202)
    - variability of behavior within, 80 (Supplement, July 136)
    - and vascular changes, 80 (Supplement, July 67-91)
  - registry for, 80 (Supplement, July 207-208)
  - unusual forms, 80 (Supplement, July 172-178)
  - ventilation mechanics in, 80 (Supplement, July 118-120)
- Emphysematous bulla *See* Bulla
- Empyema
- in pulmonary tuberculosis, 59 601-618, 78 411-425
  - tuberculous
    - alkalinization in, 66 271-284, 285-291
    - clinical course and management, 61 662-677
    - closed drainage and thoracoplasty in, 66 522-533
    - pH of, (Notes) 67 103-105

*Empyema, tuberculous cont*

- streptomycin and dihydrostreptomycin in drug concentrations attained with various vehicles, 66 271-284
  - cellugel as vehicle, 66 285-291
  - Endobronchitis, tuberculous, occult, in surgical lung specimens, 77 931-939
  - Endothelioma *See* Tumors
  - Enterocolitis tuberculous
    - acute, obstructive, treated by nonsurgical ileostomy and streptomycin, (case reports) 60 648-653
    - streptomycin in, 60 576-588
  - Enumeration technique for viable tubercle bacilli, 76 616-635
  - Enzyme(s)
    - to aid filtration of oropharyngeal washes, (Notes) 79 541
    - digestion of, in separation of *M leprae* from tissues, (Notes) 74 152
    - in meningitis, 71 12-29
    - parenterally administered, in lung abscess, 76 1-21
    - purine, in mycobacteria, (Notes) 66 240-243
    - serum, in pulmonary tuberculosis, (Notes) 79 251-252
    - of tubercle bacillus, reactions of, and the action of streptomycin, 65 722-734
    - in tuberculosis, extrapulmonary, suppurative, 71 1-11
  - Eosinophilia
    - Loffler's syndrome, (case reports) 63 480-486
    - during PAS therapy, (case reports) 70 171-175
    - with pulmonary infiltration, 59 679-686
    - and pulmonary malignancy, (case reports) 75 644-647
  - Epidemiology
    - sarcoidosis with special reference to, 62 403-407
    - of tuberculosis, 67 123-131, 68 1-8, 75 432-441
  - Epilepsy, isoniazid therapy in, hazards, (case reports) 66 501
  - Epinephrine, as bronchodilator agent, 77 729-736
  - Erle County (New York), tuberculosis case-finding program, 59 78-85
  - Erythema
    - induratum (Bazin), with tuberculous lymphadenitis, (case reports) 60 249-257
    - nodosum with tuberculin-neutralizing serum, (case reports) 62 112-115
  - Erythrocyte(s)
    - OT-sensitized sheep, and trypsinized human, serologic relation of, 79 622-630
    - sedimentation rate, in pulmonary tuberculosis, 69 595-598
    - tuberculin-treated, as antigen in eliciting cutaneous hypersensitivity to tuberculin, (Notes) 64 322-326
  - Erythromycin, in chemoprophylaxis of emphysema, 80 716-723
  - Esophageal inflation of hernial sac during pneumoperitoneum, (case reports) 75 823-827
  - Esophagobronchial fistula *See* Fistulas
  - Esophagocutaneous fistula *See* Fistulas
  - Esophagus, traction diverticula of, in middle lobe syndrome, 65 455-464
  - Estrogen(s)
    - effect
      - on progress of tuberculosis, 59 198-218
      - on tuberculin skin sensitivity and on allergy of internal tissues, 59 186-197
      - on tuberculosis in rabbits, 59 168-185
  - Ethionamide *See* Alpha-ethyl-thioisonicotinamide
  - (S)-Ethyl-L cysteine, 70 806-811
    - effect of ventilation on antituberculosis activity of, 74 68-71
    - in pulmonary tuberculosis, (Notes) 74 142-144
  - Ethyl mercaptan, antituberculosis activity of, 74 72-77
  - Ethyl-thio formyl compound, antituberculosis activity of, (Notes) 77 1017-1018
  - Europe, rehabilitation of tuberculous patients, 66 104-108
  - Eventration, transdiaphragmatic, in pneumoperitoneum, (case reports) 69 1045-1050
  - Exacerbations, post-thoracoplasty, 61 648-661
  - Excision, surgical, and lobectomy in esophagobronchial fistula, (case reports) 63 220-226
  - Exercise, and rest, in minimal pulmonary tuberculosis, 69 50-57
  - Expiratory force, index of, in ventilatory capacity tests, 78 692-696
  - Exudate, pleural, fibrin clot culture technique for isolation of tubercle bacilli from, (Notes) 80 438-440
  - Eye, tuberculosis of
    - cortisone in, study with phase contrast microscope, 74 1-6
    - in rabbits, 64 197-206, 207-217
- ## F
- Fenestration, tracheal, evolution and early results of, 79 773-779
  - Fiberglas®-plastic dust and tuberculosis, 78 512-523
  - Fibrin bodies, simulating "coin lesions," (case reports) 72 659-662
  - Fibrin-clot culture technique for isolation of tubercle bacilli from pleural exudates, (Notes) 80 438-440

- Fibrosis**  
 pulmonary  
 and bronchiolitis carcinoma, 76 559-567  
 carbon monoxide diffusing capacity in, 74 317-342  
 cardiopulmonary function in, 80 700-704  
 interstitial  
 diffuse, (case reports) 68 603-611, 71 185-510  
 Hamman-Rich syndrome, (case reports) 78 610-622  
 and hypertrophic osteoarthropathy, (correspondence), 79 513
- Fibrothorax**, tuberculous, angiopneumography and bronchography in, 73 61-71
- Filter membrane**  
 for tuberculous sputum, (Notes) 77 1019-1022  
 used in detection of tubercle bacilli in mouth wash, 71 371-381
- Fistula(s)**  
 esophagobronchial  
 associated with severe hemorrhage treated by surgical excision and lobectomy, (case reports) 63 220-226  
 in mediastinal tuberculosis, (case reports) 79 238-243  
 esophagocutaneous, treated with streptomycin and gastrostomy, 59 687-691  
 tuberculous, isoniazid-PAS in, 68 535-540
- Fitzsimons Army Hospital (Denver, Colorado)**, tuberculin reaction in tuberculous patients, 80 569-574
- Fluorescence microscopy**  
 in detection of mycobacteria in tissue sections, 68 82-95  
 of *M. tuberculosis*, 65 709-717
- Foci**, round, tuberculous, 73 805-817
- Food intake**  
 in nontuberculous patients receiving isoniazid, 68 207-211  
 of tuberculous women, 60 455-465
- Formosa (Taiwan)**, tuberculosis in, 80 359-370
- Freezing**, for preservation of stock cultures of *M. tuberculosis*, 62 99-100
- Friedländer's pneumonia**, 61 465-473
- Fume fixation of lung**, 79 764-772
- Functional residual capacity**, methods of measurement, 74 729-738
- Fungal antigens**  
 coccidioidin  
 sensitivity  
 with pulmonary calcifications, 59 643-649  
 on the Isthmus of Panama, 63 657-666  
 skin reaction in pulmonary coccidioidomycosis, (case reports) 79 78-79  
 histoplasmin  
 conversion rates in Kansas City as indication of prevalence of infection, 69 234-240  
 skin tests, effect on skin reactivity and colloidal agglutination, 66 588-593  
 sensitivity to, (correspondence) 61 269  
 in Alaskan natives, (Notes) 79 542  
 in chronic pulmonary disease, 72 274-296  
 with pulmonary calcifications, 59 643-649  
 with pulmonary infiltration, 59 636-642  
 in young school children, 78 667-681  
 urban focus of, (Notes) 79 83-86  
 histoplasmin H-42, for skin testing, (Notes) 77 546-550  
 sensitivity to, in students, 73 620-636
- Fungal disease** See Mycoses
- Fungus(s)** See also Mycoses  
 Actinomycetales  
 cultural differentiation, 76 770-788  
 isoniazid susceptibility compared with other synthetic and antimicrobial antituberculous agents, (Notes) 67 261-264
- Allescheria boydii*  
 fatal pulmonary infection with, (case reports) 78 604-609  
 in sputum, (case reports) 71 126-130
- Aspergillus fumigatus*, significance in sputum, 80 167-180
- Aspergillus* infestation, with cystic disease, (case reports) 74 92-98
- Blastomyces dermatitidis* as antigen for polysaccharide skin test, 77 983-989  
 and *Histoplasma capsulatum*, polysaccharide skin tests on humans, (Notes) 80 264-266
- Candida albicans*  
 and adjuvants, sensitization of guinea pigs, (Notes) 76 692-696  
 detection, on culture media of *M. tuberculosis*, 75 836-840  
 in tuberculous sputum, (Notes) 77 543-545
- Coccidioides immitis*  
 hyphae of, in human tissues, 70 320-327  
 immunization against, 74 245-248  
 experimental, 70 498-503  
 isoniazid-iproniazid effect, (Notes) 67 538  
 sporulation inhibited by peptone, (Notes) 74 147-148
- Cryptococcus neoformans*, causing pulmonary lesion, 74 441-444
- Histoplasma capsulatum*  
 as antigen for polysaccharide skin test, 77 983-989  
 and *Blastomyces dermatitidis*, polysaccharide skin tests on humans, (Notes) 80 264-266  
 isolation from sputum, 66 578-587  
 laboratory infection, (Notes) 72 690-692  
 in *Macacus irus* monkeys, (Notes) 75 849-851

*Fungus(s), Histoplasma capsulatum, cont*

- pulmonary cavitation caused by, (case reports) 69 111-115
- reactions to, in rabbits, 62 374-389

*Nocardia*

- characterization of species, 76 451-479
- cultural differentiation, 76 770-788

*Nocardia asteroides*, PPD and other antigens prepared from, 79 284-295

- pathogenic, and yeasts, culture filtrates of, tuberculostatic properties of, (Notes) 66 623-625

- in pulmonary diseases in India, (Notes) 78 644-646

**G***Gamma globulin*

- in childhood tuberculosis, 74 15-28
- content of serum in pulmonary tuberculosis, (correspondence) 61 893-894

*Gas* See also Pulmonary function*exchange*

- and pulmonary circulation, influence of ventilatory mechanics on, 80 53-58
- and respiratory ventilation in chronic pulmonary emphysema, mechanical respirators in, 80 510-521
- intrapulmonary, mixing after lobectomy, 78 1-7
- mixing in tuberculous lung, 74 343-350
- in tuberculous cavities, 80 1-5

*Gastric aspiration for culture of M tuberculosis*, 67 598-603*Gastric dilatation after phrenic nerve interruption*, (case reports) 62 331-332*Gastric lavage*

- culture for *M tuberculosis*, trisodium phosphate transport-digestion method of processing specimens, (Notes) 70 363-366
- and laryngeal swabs in isolation of tubercle bacilli, 73 930-939
- method of obtaining, 60 228-235
- pancreatin-quaternary ammonium treatment, 74 616-621

- for tubercle bacilli, evaluation of four methods of collecting and mailing, 65 617-626

*Gastric tuberculosis* See Tuberculosis, gastric*Gastric washings* See Gastric lavage*Gastrointestinal changes in pneumoperitoneum*, 66 750-757*Gastrostomy, in esophagocutaneous fistula*, 59 687-691*Gelatin foam, in thoracoplasties*, 61 193-200*Gel-diffusion techniques*

- precipitation, in tuberculosis, 77 450-461
- with tuberculin antigens, 75 601-607

- tests for tuberculosis, 80 886-894
- double-, 80 152-166

*Genetic resistance to tuberculosis in rabbits*, 72 297-329*Genitourinary tuberculosis* See Tuberculosis, genitourinary*Georgia*

- compulsory isolation of tuberculous patients, (Notes) 77 506-510
- tuberculosis studies in Muscogee County, 73 157-164

*Geotrichosis* See Mycoses*Germany, tuberculosis in*, 59 481-493*Globulin titration*

- in demonstration of circulating antibodies after BCG immunization, (Notes) 78 793
- technique in tuberculosis, (correspondence) 76 507-508

*Glucose*

- effect on tuberculin reaction in tissue culture, 78 712-724

- metabolized by *M smegmatis*, (Notes) 73 589-592

- and oxygen, in autolysis of *M tuberculosis*, 73 907-916

- transfer of, into cerebrospinal fluid in tuberculous meningitis, 67 732-754

*Glucosulfone activity on H37Rv strain of M tuberculosis*, 59 461-465*D-Glucuronolactone isonicotinyl hydrazide-isoniazid*, inhibitory activity, 73 892-906*Glutamic acid*, affect on mycobacteria, (Notes) 75 688-691*Glutamic ovalacetic transaminase*, in pulmonary tuberculosis, (Notes) 79 251-252*Glutamic pyruvic transaminase*, in pulmonary tuberculosis, (Notes) 79 251-252*Glycerol*

- containing zinc, (Notes) 74 145-146
- effect on growth of *M tuberculosis*, 74 50-58

*Glycoprotein of serum in tuberculous guinea pigs*, 68 594-602*Goiter following PAS therapy*, (case reports) 69 458-463*Gold (Au<sup>199</sup>)*

- radioactive, for determining lymphatic draining of pericardium, (Notes) 76 906-908
- in study of lymphatic drainage in dogs, (Notes) 75 145-147

*Gold miners, silicotic, lung function in*, 77 400-412 (See also Pulmonary function)*Gonadotropin*

- chorionic, effect on tuberculosis in rabbits, 59 168-185

- effect on progress of tuberculosis, 59 198-218

*Grafts, bone, homogenous, ribs from thoracoplasty as possible source of*, 63 210-212

Granulocytes in attempt to transfer tuberculin type of sensitivity, 64 516-519

Granuloma coccidioidii *See* Mycoses and Tumors

Granulomatosis *See also* Pneumococcoses and Wegener's granuloma

allergic, and Wegener's, distinction between, (correspondence) 70 544-545

pathergic, of lungs, 78 21-37

Great Britain, irregular discharge in, (correspondence) 69 847-851

Guillain Barré syndrome after PAS, (case reports) 69 455-457

Guinea pig(s) *See also* Tuberculosis, experimental

4 acetylaminobenzil thiosemicarbazone (Tibione) in tuberculosis of, 62 141-155

BCG infection, cortisone in, 69 511-519

BCG vaccine and hyaluronidase in, 68 188-198

corticotropin-cortisone in, 64 295-306

cortisone in tuberculous lesions of, 62 337-344

in detection of tubercle bacilli

compared with mice and artificial media, 69 92-103

from dispersed cultures, 65 572-588

with discrete chronic tuberculous lesions, streptomycin in, 66 191-212

in experimental tuberculosis

antituberculosis drug screening in, 68 48-64

cortisone-dihydrostreptomycin in, (Notes) 67 101-102

dissemination of tubercle bacilli, 61 399-406

effect of dihydrostreptomycin-PAS on, 62 149-155

irradiated antituberculosis vaccine and BCG in, 67 341-353

isoniazid in, 68 75-81

neomycin in, 62 300-306, 345-352

serum glycoprotein in, 68 594-602

streptomycin in, 68 575-582

treated with isoniazid, 65 365-375, 376-391

treated with potassium iodide-streptomycin, 66 680-698

treated with pyrazinamide, 65 519-522

immunogenicity for, of BCG cultured in bile, 59 102-105

inoculation, for detection of tubercle bacilli, limitations of, (correspondence) 70 374-375

inoculation versus culture on artificial media, (Notes) 72 687-689

intradermal tuberculin reaction on, 69 806-817

omentum used as index in chemotherapy, 68 583-593

potassium iodide-streptomycin in, 64 102-112

sensitization, mycobacterial wax in, 69 241-246

streptomycin-PAS in intracerebral infection of, 64 87-101

tuberculous

abortive tuberculosis induced in by pathologic material containing young tubercle bacilli, (correspondence) 68 167

pyrazinimide in, (Notes) 70 367-369

serum protein in, 70 311-318

thiouracil, substituted in, 70 130-138

tuberculous meningitis in

isoniazid, iproniazid, streptomycin, and streptomycin-isoniazid in, 70 714-727

produced by lumbar intrathecal inoculation, 66 722-731

virulence

correlated with catalase activity and isoniazid resistance, (Notes) 72 246-251

of isoniazid resistant cultures in, (Notes) 68 290-291

of isoniazid resistant tubercle bacilli in, (Notes) 69 461-468

## II

Hamartoma *See* Tumors

Hamman-Rich syndrome, 71 485-510

cortisone in, (case reports) 76 123-131

pathogenesis of, 78 353-367

report of three cases, (case reports) 78 610-622

Hand talking chart, (correspondence) 70 534-535

Hawaii

resection for pulmonary tuberculosis in, 80 6-11

tuberculosis in, 68 839-862

Heart

atherosclerosis, (symposium) 71 904-924

block, change in tuberculosis of myocardium, (case reports) 65 332-338

disease, Beck operations for (symposium), 71 904-924

involvement in military tuberculosis, (case reports) 68 771-774

symptoms in tuberculosis, 62 (Supplement, July 98-103)

tuberculosis of, 62 390-402

"Heaves" *See* Emphysema, alveolar, chronic

HeLa cells *See* Cells

Helium dilution method

closed-circuit, in measuring functional residual capacity, 74 729-738

in ventilation study, 79 450-456

Hemagglutination

procedure in study of tuberculins, 65 272-277

reaction

after BCG, 66 58-62

antiglobulin modification of, 68 739-745

clinical evaluation of, 67 497-502

in tuberculosis

in children, 70 139-148

diagnosis of, 64 71-76

*Hemagglutination cont*

- test
  - for antibodies, 65 194-200
    - and its hemolytic modification in tuberculosis, 65 194-200, 66 594-600
  - complement-fixation modification (Maillard) of, in tuberculosis, (Notes) 66 621-622
  - Middlebrook-Dubos, clinical interpretation, 62 121-127
  - modification of slide test for antibodies against tubercle bacilli, 63 667-671
  - in tuberculosis, (editorials) 62 223-226
- Hemagglutinin adsorption, specificity of, in serologic study of tuberculosis, 67 657-664
- Hemangiopericytoma *See* Tumors
- Hemangio sarcomatosis *See* Tumors
- Hematoma *See* Tumors
- Hemidiaphragm, paralyzed, effect on homolateral thoracoplasty, 60 183-188
- Hemin
  - antagonism of isoniazid, (Notes) 69 469-470
  - as growth factor in isoniazid-resistant strains of *M tuberculosis*, 69 797-805
- Hemoglobin, and methemoglobin, values in tuberculous patients on isoniazid therapy, (Notes) 68 286-289
- Hemolytic and hemagglutination tests in tuberculosis, 66 594-600
- Hemopneumothorax, spontaneous, 62 543-548, (case reports) 65 744-753
  - benign, 63 417-426
  - surgery for, 71 30-48
- Hemoptysis, in chest clinic patients, 63 194-201
- Hemorrhage(s)
  - in emphysematous bulla, (case reports) 61 742-746
  - intraperitoneal, occurring as a complication of pneumoperitoneum, 63 116-118
  - fatal, in pulmonary tuberculosis, 60 589-603
  - pulmonary, in tuberculosis, (case reports) 62 324-330
  - pneumectomy for, (case reports) 61 426-430
- Hemothorax
  - spontaneous, (case reports) 71 755-761
  - in therapeutic pneumothorax, (case reports) 50 654-659
- Hepatitis
  - choleangiolitic, due to PAS, (case reports) 76 132-139
  - and hypokalemia in tuberculosis, (case reports) 68 136-143
  - post-transfusion, with sickle-cell anemia, (case reports) 67 247-257
  - pyrazinamide in, serum enzymes in, 80 855-865
  - pyrazinamide induced, (case reports) 77 853-862
- Hepatolysis, in pneumoperitoneum, (case reports) 69 297-299
- 5-Heptyl-2-thiohydantoin in experimental tuberculosis, 78 74-82
- Hernia
  - esophageal, hiatal, pneumoperitoneum in, (case reports) 78 623-631
  - inguinal, pneumoperitoneum in, (case reports) 60 524-526
- Heterocyclic acid hydrazides *See* Acids
- n-Hexadecane as adjuvant for BCG in mice, 75 624-629
- H<sub>1</sub> Intensity ultraviolet for sterilization, (Notes) 71 457-458
- Hilum, triangular shadows of, 66 188-193
- Hinconstarch
  - antituberculosis activity, 73 72-78
  - metabolic products, (Notes) 74 798-801
  - in pulmonary tuberculosis, 73 219-228, 77 952-967
  - seromucoid (serum mucoprotein) values, (Notes) 78 131-134
- Histidine, utilization of, in production of a pharmacologically active metabolite, 63 100-107
- Histiocytosis X, pulmonary, (case reports) 75 319-325
  - with diabetes insipidus, (case reports) 79 652-658
- Histoplasma capsulatum* *See* Fungi
- Histoplasmin *See* Fungal antigens
- Histoplasmin H-42 *See* Fungal antigens
- Histoplasmosis *See* Mycoses
- Home, and hospital, in tuberculosis, including chemotherapy of, 80 (Supplement, October 23-45)
- Hong Kong, tuberculosis in, and BCG, 76 215-224
- Honolulu schools, tuberculin testing in, 78 871-883
- Hooke's law, application to elastance of lung, (Notes) 77 863-866
- Hormones(s)
  - adaptive, request for reprints on stress and, (correspondence) 67 677-678
  - adrenal, in experimental ocular tuberculosis, 66 175-186
  - corticosteroids and corticotropin in tuberculosis, 76 708-710
  - corticotropin
    - as adjuvant in tuberculosis, 76 708-710
    - dihydrostreptomycin, in experimental bovine tuberculosis in rabbit, 76 201-211
    - in emphysema, effect on pulmonary function, 64 279-294
    - in pneumonia induced with tuberculin in lungs of sensitized rabbits, 64 508-515
    - streptomycin-PAS, in pulmonary tuberculosis, 66 542-547
    - in tuberculosis, 66 161-174
    - experimental, (Notes) 77 536-538

*Hormones(s) corticotropin, cont*

- compared with cortisone, 68 31-41
  - with and without antimicrobial therapy, 70 623-636
  - in humans, request for data, (correspondence) 64 471-472
  - in infancy and childhood, 74 (Supplement, August 209-216)
  - ocular, decreasing dosages in the rabbit, (Notes) 69 1051-1053
  - in tuberculous lesions in guinea pig, 64 295-306
  - in tuberculous meningitis, (case reports) 72 825-832
- cortisone**
- in BCG infection in guinea pig, 69 511-519
  - in cardiopulmonary function in Boeck's sarcoid, 67 154-172
  - in corneal tuberculosis, 74 1-6
  - dihydrostreptomycin, in experimental tuberculosis in guinea pig, (Notes) 67 101-102
  - effect on electrophoretic patterns and hemagglutination reaction in childhood tuberculosis, (Notes) 73 964-965
  - in emphysema, effect on pulmonary function, 64 279-294
  - in experimental tuberculosis, 62 337-344, 65 64-74, 596-602, 603-611
    - in albino rats, compared with alloxan-induced diabetes, 65 603-611
    - compared with corticotropin, 68 31-41
    - growth of tubercle bacilli after, (Notes) 77 529-535
  - in Hamman-Rich syndrome, (case reports) 76 123-131
  - isoniazid in BCG-vaccinated subjects, 76 263-271
  - streptomycin in experimental tuberculosis in albino rats, 65 596-602
  - in tuberculosis, 66 161-174
    - with and without antimicrobial therapy, 70 623-636
    - in humans, request for data, (correspondence) 64 471-472
    - in infancy and childhood, 74 (Supplement, August 209-216)
  - in tuberculous lesions in guinea pigs, 64 295-306
  - in tuberculous meningitis, 64 564-571, (case reports) 73 99-109
  - in experimental tuberculosis in mice, 69 790-796
- hydrocortisone**
- acetate ointment
    - topical, at site of intracutaneous tuberculin reaction, (Notes) 79 666-668
    - in tuberculin skin reaction, (Notes) 80 587-589

- prednisone
    - causing tuberculosis activation, (case reports) 76 140-143
    - in pleural tuberculous effusions, 79 307-314
  - somatotropic
    - effect on course of tuberculosis in rabbit eye, 69 1016-1021
    - in tuberculosis, (correspondence) 71 319-321
  - testosterone, in chronic pulmonary tuberculosis, 68 165-176, 70 1020-1029
- Horner's syndrome complicating surgery for pulmonary tuberculosis, 67 94-100**
- Horse, chronic alveolar emphysema in, 80 (Supplement, July 141-143)**
- Hospital(s) See also Sanatoriums**
- discharges See Discharges
  - Fitzsimons Army Hospital (Denver, Colorado), tuberculin reaction in tuberculous patients, 80 569-574
  - general, case finding in, 70 304-311
  - and home, in tuberculosis, and chemotherapy, 80 (Supplement, October 23-45)
  - military, for tuberculosis, histoplasmosis in, (Notes) 75 833-835
  - personnel, tuberculosis control in, 67 74-84
  - for tuberculosis
    - case finding in, 80 (Supplement, October 73-93)
    - employees, tuberculosis among, 66 16-27
    - isolation of air-borne tubercle bacilli in, (Notes) 67 878-880
    - rehabilitation and occupational therapy in, 79 680
    - vocational rehabilitation in, justification of, 80 59-64
  - tuberculous patients in, adjustment on various wards, 79 273-283
- Household associates, tuberculosis attack and death rates of, 65 111-127**
- Humoral factors in resistance to tuberculosis, 76 90-102, 78 884-898**
- Hyaluronidase**
- effect on BCG vaccination, 64 442-447, 68 188-198
  - in tuberculosis, 63 108-115
- Hydrazines in production of fatty livers in rabbits, (Notes) 73 956-959**
- Hydrocortisone See Hormones**
- Hydrogen peroxide**
- isoniazid, *M. paratuberculosis* susceptible and resistant to, differential uptake of isoniazid-C<sup>14</sup> by, (correspondence) 80 110-111
  - in isoniazid resistance, 73 726-734
- Hydroxyethyl sulfone in pulmonary tuberculosis, 68 103-118**
- Hyperergic reactivity, nonspecific, at site of tuberculin reaction, 69 205-215**



- Hyperplasia, lymph node, of mediastinum, (case reports) 79 232-237
- Hypertension, terminal, with sarcoidosis, (case reports) 60 228-235
- Hyperthyroidism in native resistance to tuberculosis, 79 152-179
- Hypothyroidism in native resistance to tuberculosis, 79 180-203
- Hyperuricemia, during pyrazinamide-isoniazid therapy, (Notes) 74 289-292
- Hypnosis, bronchograms under, (Notes) 79 525
- Hypogammaglobulinemia, with steatorrhea and probable tuberculosis, (case reports) 74 773-782
- Hypokalemia and hepatitis in tuberculosis, (case reports) 68 136-143
- Hyponatremia in pulmonary tuberculosis, 66 357-363
- Hypopotassemia in pulmonary tuberculosis, 66 357-363
- Hypoventilation, idiopathic, polycythemia, and cor pulmonale, (case reports) 80 575-581
- Hypoxia, from pulmonary emphysema, hematologic adaptation in, 78 391-398
- I**
- $I^{131}$ , radioactive, -labeled 3,5 diodo PAS, effect on tubercle bacillus, 65 316-324
- Icterus, in milary tuberculosis, (case reports) 66 77-85
- Ileostomy, nonsurgical, in tuberculous enterocolitis, (case reports) 60 648-653
- Immobilizer, lung, in pulmonary tuberculosis, (correspondence) 67 267, 778-780
- Immunity *See* Tuberculosis, immunity
- Immunology and pulmonary diseases, 79 212-220
- Immunopathology of tuberculosis, 74 (Supplement, August 60-74)
- Index of air velocity *See* Ventilatory function and Pulmonary function
- Index card, for clinical data on patients in a tuberculosis hospital, (Notes) 70 903-906
- Indians (American), tuberculous infection in, 72 35-52
- Industry, roentgenograms in, 60 501-513
- Infant(s)
- pulmonary tuberculosis in, Promizole®-streptomycin in, (case reports) 61 747-750
  - tuberculous infection in, (case reports) 70 161-165, (Notes) 74 149-151, (correspondence) 80S-809
- Infarction, pulmonary, location of, 60 206-211
- Influenza *See* Viruses
- Infrared spectrums of fractions of *M. tuberculosis*, 65 477-480
- Inhalation treatment, (editorials) 74 454-456
- Inhibition of tubercle bacilli, tested in synthetic organic bases, (Notes) 65 631-634
- Inoculation, cutaneous, tuberculosis from, 63 526-537
- Inoculum, size in susceptibility testing of *M. tuberculosis*, (Notes) 72 390-392
- Inspissated cavities *See* Cavities
- Insulin, in treatment of anorexia, 60 25-31
- Intermittent positive pressure breathing
- in bronchopulmonary disease, 71 693-703
  - in emphysema, pulmonary, severe, 76 33-46
  - in pulmonary tuberculosis, 72 479-486
- International Symposium of the Deborah Sanatorium and Hospital, 80 (Supplement, October 1-139)
- International Union Against Tuberculosis, (correspondence), 78 810, report on, 77 155-161
- Intestinal tuberculosis *See* Tuberculosis, intestinal
- Intraperitoneal hemorrhage *See* Hemorrhages
- Iodine
- in leprosy, (correspondence) 68 295-296
  - in tuberculosis, (correspondence) 66 765-777
- Iodized oil in bronchography in pulmonary tuberculosis, 66 699-721
- Ions, ammonium, effect on ability of virulent mycobacteria to bind neutral red, (correspondence) 60 384
- Isoniazid
- in *Coccidioides immitis*, (Notes) 67 538
  - discontinuance, withdrawal symptoms, 67 212-216
  - in murine leprosy, (Notes) 67 674-675
  - neurotoxicity in dogs, 69 261-266
  - pharmacology, 68 199-206
  - resistance of mycobacteria to, (Notes) 65 754-758, 759-760, 768-770
  - in sarcoidosis, ineffectiveness of, (Notes) 67 671-673
  - side effects of, (Notes) 68 270-272
  - in tuberculosis
    - experimental, 65 365-375, 376-391
    - human, 65 402-428  - in tuberculous meningitis, 70 714-727
- Iron distribution in tuberculous granulation tissue, 61 560-562
- Irradiation, by sunlamp, effect on *M. tuberculosis*, 71 112-125
- Irregular discharge *See* Discharges
- Isolation, compulsory, of uncooperative patient, (Notes) 77 506-510
- Isoniazid
- absorption, 65 429-442
  - Actinomycetales susceptibility to, compared with other synthetic and antimicrobial agents, (Notes) 67 261-264

## Index of

- action
  - antithyroid, (Notes) 71 889-891
  - on intracellular tubercle bacilli, 66 125-133
  - mode of, 70 781-792, (correspondence) 75 517-518
- activity
  - alone, and in combination with streptomycin, 67 808-827
  - neutralization of, by metabolites, 73 735-747
- allergy, (case reports) 71 783-792
- alone
  - and with PAS, in original chemotherapy of noncavitary pulmonary tuberculosis, 80 611-647
  - in pulmonary tuberculosis, 71 903-916
  - and combined with streptomycin, 67 808-827
- antagonism
  - by antibacterial agents, (Notes) 68 250-253
  - by certain metabolites, (Notes) 68 938-939
  - delayed by pyridoxine *in vivo*, (Notes) 76 1100-1105
- antithyroid action, (Notes) 71 889-891
- antituberculosis action, (Notes) 77 364-367
- bacterial resistance to, streptomycin effect, 67 553-567
- bactericidal action on extracellular and intracellular tubercle bacilli, 67 322-340
- bacteriotropic activity with other compounds, (Notes) 78 802-805
- bacteriotropic potencies increased by PABA, (correspondence) 78 949-951
- in biologic fluids, (Notes) 65 184-185
- breakdown, peroxide in, (Notes) 73 779-780
- C<sup>14</sup>
  - differential uptake by *M. paratuberculosis* susceptible and resistant to isoniazid and hydrogen peroxide, (correspondence) 80 110-111
  - labeled PAS, 75 71-82
- catalase and peroxidase relation in mycobacteria, 75 62-70
- cavities in tuberculosis treated with, 77 221-231
- central nervous system reactions to, 69 759-762
- as chemoprophylactic in tuberculosis, (correspondence) 71 475-476
- clinical evaluation of, (correspondence) 70 1102-1103
- in combined chemotherapy of mice, 68 411-418
- compared with streptomycin-isoniazid, and streptomycin-PAS in pulmonary tuberculosis, (Notes) 66 632-635, 68 264-269, 67 108-113, 539-543
- concentrations
  - in blood of people of Japanese and European descent, (Notes) 78 944-948
  - in culture media, effect of inspissation and storage on, (Notes) 75 678-683
  - in tuberculous patients, effect of amines on, (Notes) 76 152-158
- cortisone, in BCG vaccinated subjects, 76 263-271
- cycloserine
  - in ambulant tuberculosis therapy, (Notes) 89 91
  - in pulmonary tuberculosis, (Notes) 79 87-89
  - high dosage, treatment-failure, chronic (Notes) 80 269-273
  - in tuberculosis, 75 553-575
- D glucuronolactone isonicotinyl hydrazide, inhibitory activity of, 73 892-906
- delirium and, (correspondence) 69 845-846
- dependent strains of *M. ranac*, (Notes) 68 631-633
- derivatives, in experimental tuberculosis, 67 354-365
- determination of
  - in body fluids, 76 852-861
  - by urine tests, (Notes) 80 904-908
- in development of atypical variants of *M. tuberculosis in vitro*, (Notes) 78 921-926
- discontinuance, withdrawal symptoms, 67 212-216
- distribution, 65 429-442
- dosage, high
  - in man, 69 957-962
  - in pulmonary tuberculosis, (Notes) 77 539-542
- early treatment in tuberculosis in guinea pigs, 76 732-751
- effect
  - on allergy, 74 (Supplement, August 197-208)
  - on bacillary metabolism, 80 404-409
  - of barbiturates on toxicity of, (Notes) 66 100-103
  - on BCG allergy, 77 232-244
  - on *Coccidioides immitis*, (Notes) 67 538
  - on diabetes, (correspondence) 67 544
  - emotional, 68 523-534
  - and electro encephalographic, 70 476-482
  - on immunizing activity of normal and isoniazid-resistant BCG, (Notes) 75 650-655
  - inhibitory, on growth of tubercle bacilli antagonized by ketone compounds, (Notes) 68 273-276
  - on mycobacterial lipids, 72 713-717
  - on nitrogen metabolism and food intake in nontuberculous patients, 68 207-211
  - on program of tuberculosis associations, (editorials) 66 615-618
  - on pyridoxine metabolism, 75 594-600
  - on tubercle bacilli, growing and resting, (Notes) 69 125-127
  - growth of, from pulmonary lesions, (Notes) 79 518-521

*Isoniazid, effect cont*

- phase contrast and electronmicroscopic studies of, (Notes) 73 296-300
- proposed mechanism for, (correspondence) 69 1062
- in vitro*, 71 556-565
- on tuberculin reaction and healing of BCG-induced ulcers, 71 7-11
- on tuberculin test, (Notes) 67 535-537
- on viability of *M. tuberculosis*, 69 1022-1028
- excretion, 65 429-442
- and fever, (case reports) 68 219-252
  - transitory, and roentgenographic exacerbation from, (case reports) 72 527-536
- hydrazones, in biologic fluids, 79 192-496
- inactivation
  - by Dubos medium, (Notes) 68 284-285
  - by mycobacterial extracts, 72 196-203
- ineffectiveness in microbial persistence, (Notes) 76 1106-1109
- ingestion indicated with riboflavin, (Notes) 80 415-423
- inhibition of, in man, by PAS and benzoyl-PAS, 80 26-37
- and isoniazid-streptomycin, in tuberculosis, incidence of bacterial resistance, (Notes) 67 106-107
- isopropyl derivative *See* Iproniazid
- low concentrations measured by microbiologic assay technique, (Notes) 75 992-994
- metabolism of
  - by *M. tuberculosis* BCG, (Notes) 78 806-809
  - and peripheral neuritis, 70 266-273
  - serum microbiologic assay technique for, (Notes) 75 995-998
  - and sputum conversion, (correspondence) 77 869-871
- in multiple sclerosis, 70 577-592
- in murine leprosy, (Notes) 67 674-675
- neurotoxicity in dogs, 69 261-266
- neutralization by pyridoxal, 76 568-578
- paired with other drug combinations, 80 627-640
- PAS
  - compared with pyrazinamide-isoniazid, 73 704-715
  - effect on thyroid function, 80 845-848
  - salt of, in tuberculosis, (Notes) 78 637-643
  - single daily dose, 78 749-759
  - in tuberculous sinuses and fistulas, 68 535-540
- peripheral neuritis associated with, (case reports) 70 504-508
- peripheral neuropathy in patients treated with, (case reports) 68 458-461
- pharmacology of, 67 644-651, 68 199-206
- in presence of PABA, (correspondence) 76 706-707
- prevention, in experimental tuberculosis, 74 917-939
- in production of fatty livers in rabbits, (Notes) 73 956-959
- prophylaxis
  - effect on tuberculin response, 77 232-241
  - in experimental tuberculosis, (Notes) 77 999-1004
  - in guinea pigs, 73 1-18
  - in nontuberculous disease, (correspondence) 78 485-487
- psychosis, toxic, from, (case reports) 79 799-804
- pyrazinimide,
  - causing hyperuricemia, (Notes) 74 289-292
  - compared with isoniazid-PAS, 73 704-715
  - hepatotoxicity of, in tuberculosis, 80 371-387
  - in low dosage, 74 400-409
  - in patients with previous isoniazid therapy, (Notes) 75 846-848
  - in tuberculosis, (Notes) 72 851-855
  - experimental, 69 319-333
  - pulmonary, 69 319-350, 70 413-422, (Notes) 70 713-747
- pyridoxine
  - concurrently administered, (Notes) 74 471-473
  - effect on antituberculosis activity of, *in vivo*, (Notes) 71 898-899
  - relationship in children, 75 594-600
- radioactive, action on tuberculosis, 67 491-496
- resistance
  - acquired, (Notes) 79 97-101
  - and catalase activity
    - correlated with guinea pig virulence, (Notes) 72 246-251
    - of tubercle bacilli, (Notes) 69 471-472
  - catalase and hydrogen peroxide in, 73 726-734
  - intra strain variation, 73 390-405
  - of mycobacteria to, (Notes) 65 754-774
  - to *M. avium*, (Notes) 77 519-523
  - in pretreatment patients, 72 143-150
  - in relation to pyrogallol-peroxidative activity in *M. tuberculosis*, (Notes) 75 670-674
- resistant
  - cultures, from clinical specimens, virulence of, in guinea pigs, (Notes) 68 290-294
  - mutants, 70 465-475
  - organisms, tuberculous pneumonia due to, (case reports) 70 881-891
- strains of *M. tuberculosis*
  - peroxide formation in medium for, 75 476-487
  - virulence, 71 799-809
- tubercle bacilli, 70 91-101, 442-452
  - altered growth characteristics of, (Notes) 66 626-628
  - growth requirements of, (correspondence) 75 155-156
  - catalase and pathogenicity of, 70 641-664
  - hemin as growth factor for, 69 797-805

*Isonia id, resistant, cont*

- in infection of children, 80 326-339
- lesions produced by, regression of, (Notes) 70 531-532
- metabolism of, 71 785-796
- pathogenicity of, in children, 74 (Supplement, August 75-89)
- human, 71 390-405
- pathology of lesions caused by, (Notes) 74 633-637
- in pulmonary tuberculosis, new and untreated, (Notes) 74 293-296
- superinfection with, (case reports) 77 168-171
- virulence of, 68 548-556, (correspondence) 69 640-641, (correspondence) 70 375-376, 70 728-733
- in guinea pigs and mice, (Notes) 69 464-468
- immunizing properties compared with BCG, (Notes) 70 527-530
- Salizid®, in the blood, (Notes) 74 796-797
- in sarcoidosis, ineffectiveness of, (Notes) 67 671-673
- serum concentrations
  - and therapeutic response, correlation of, in pulmonary tuberculosis in humans, (correspondence) 80 108-110
  - in tuberculous patients, (Notes) 68 286-289
- serum-free, chemical and biologic determination method, 79 344-350
- singly, in murine leprosy, (Notes) 72 846-850
- stability, 71 732-742
- streptomycin
  - action of *M. tuberculosis* within phagocytes, (Notes) 65 775-776
  - antagonism in mice infected with *M. tuberculosis* H37Rv, (Notes) 68 277-279
  - in experimental tuberculous meningitis, 70 714-717
  - in murine leprosy, (Notes) 72 846-850
  - resistance, (correspondence) 75 346-347
  - synergism of, *in vitro*, (Notes) 65 777-778
  - therapy, in fatal meningitis, (case reports) 72 653-658
  - in tuberculosis
    - experimental, in guinea pigs, 68 575-582
    - ocular, in rabbits, 69 1016-1021
    - PAS, combinations of
      - therapeutic and toxic effects of, 69 1-12
      - in tuberculosis, 32-week observations on, (Notes) 70 521-526
    - viomycin-streptomycyclidene isonicotinyl hydrazine, in mouse, (Notes) 68 292-294
- streptovaricin
  - controlled clinical trial of, (Notes) 80 757-759
  - in pulmonary tuberculosis, (Notes) 80 424-425, 431-433
- surgical pathology of pulmonary tuberculosis treated by, (Notes) 68 144-149
- susceptible and -resistant *M. tuberculosis* strains, catalase and peroxidase activities of, (Notes) 79 669-671
- susceptibility and pathogenicity of tubercle bacilli, 68 734-738
- therapy
  - in epileptics, hazards of, (case reports) 66 501
  - in tuberculous meningitis, (case reports) 73 940-943, (correspondence) 74 480
- thiocarbanidin, in pulmonary tuberculosis, (Notes) 80 590-593
- toxic psychosis from, (case reports) 79 799-804
- toxicity of, (correspondence) 68 296-297
  - accompanied by leukopenia and lymphocytosis, (case reports) 69 824-828
  - high dosage, 70 430-441
  - and metabolic effects of, in adults, 67 652-656
  - for monkeys, (correspondence) 68 470
  - for rhesus monkey, 67 798-807
  - short-term, 65 429-442
- trace metals in inhibition of bovine liver, catalase by, (Notes) 77 501-505
- tuberculin reactions during treatment with, 69 733-744
- in tuberculosis
  - experimental, 65 357-364, 365-375, 376-391, 392-401, 73 1-18, 75 295-302
  - in guinea pigs, 68 75-82
    - infected with tubercle bacilli resistant to streptomycin-PAS, 66 477-485
  - pyridine nucleotides before and during, 70 453-464
  - reinfection in, (Notes) 79 246-250
  - in vivo*, affected by "anti-isoniazid" substance, (Notes) 73 764-767
  - fibrocaseous, sputum culture and microscopy during treatment, 70 349-359
  - human, 65 402-428, 429-442
  - isolation, drug-susceptibility, and catalase testing of tubercle bacilli from patients, 70 852-872
  - meningeal and military, 66 391-415
  - primary, prophylactic effects of, 76 942-963
  - pulmonary, (correspondence) 70 924-925, (correspondence) 71 314-315, (Notes) 73 117-122
  - adrenal cortical function during treatment, 70 841-851
  - cystlike cavities during therapy, (Notes) 69 1054-1056
  - and electrophoretic serum proteins, 70 334-343
  - lesions, pathology of, 71 186-192

*Isoniazid, in tuberculosis cont*

- long term, 70 228-265
- in monkeys, 71 (Supplement, August 138-153)
- prior to resection, 70 102-108
- with pyrazinamide or PAS, (Notes) 79 102-104
- of recent origin, 71 841-859
- tuberculostatic action, antagonized by hemin, (Notes) 69 469-470
- in tuberculous adenitis, (Notes) 74 136-141
- in tuberculous meningitis
  - deleterious effect possible, (correspondence) 71 765-766
  - experimental, 70 714-727
  - in tuberculous sinuses and fistulas, 68 535-540
  - in vitamin E deficiency, 80 223-231
- Isonicotinic acid, hypothesis of antituberculosis action of isoniazid, (Notes) 77 364-367
- Isonicotinic acid hydrazide *See* Isoniazid
- Isonicotinyl salicylidene hydrazine, and isoniazid in the blood, (Notes) 74 796-797
- Israel, mass roentgenography among immigrants to, (Notes) 69 837-840
- Ivalon sponge plombage, (Notes) 78 478-484

**J**

- Jaundice *See* Icterus
- Jejunum, hemorrhage into, from abdominal aorta through tuberculous lymph nodes, (case reports) 65 210-214
- Jews, tuberculosis among, 67 85-93
- Johnin
  - fractionation of, 68 444-450
  - PPD, cattle erythrocyte sensitization with, (Notes) 77 177-186

**K****Kanamycin**

- in murine leprosy, (Notes) 79 673-676
- in *M. tuberculosis*, (Notes) 78 138-139
- in humans, 79 72-77
- in vitro* and in guinea pigs, antituberculosis activity of, 79 66-71

**Kansas City**

- histoplasmin conversion rates as indication of prevalence of infection in, 69 234-240
- tuberculin conversion rates as indication of prevalence of infection in, 69 227-233
- Ketone compounds, effect on inhibition of growth of tubercle bacilli by isoniazid *in vitro*, (Notes) 68 273-276

**Kidney(s)**

- epithelial cells, sensitivity to PPD and other culture filtrates, 80 410-414

- pyrazinamide spectrophotometric determination in, 75 105-110
- tuberculosis of *See also* Tuberculosis, renal
  - roentgenographic classification of, 67 604-612
  - viomycin effect on function, 68 541-547
- Kojic acid *See* Acids
- KPAS *See* Potassium para aminosalicylate

**L****Laboratory (ies)**

- design and operation for experimental tuberculosis, 68 212-219
- in tuberculosis sanatorium, (editorials) 73 291-293

**Laryngeal swabs**

- for culture of *M. tuberculosis*, 67 598-603
- and gastric lavage, in isolation of tubercle bacilli, 73 930-939

**Larynx**

- carcinoma of, with bronchogenic carcinoma, (case reports) 74 438-440
- nerves of, recurrent paralysis as complication of pulmonary tuberculosis, (case reports) 65 93-99

**Lavage**

- gastric and tracheal, compared in culture of *M. tuberculosis*, 68 926-932
- tracheal, in diagnosis of pulmonary tuberculosis, 60 634-638

**Leprosy**

- experimental, chemotherapy of, evaluation of drugs, 69 173-191
- iodine in, (correspondence) 68 295-296
- murine
  - chemotherapy of, 60 359-365
  - evolution of, (Notes) 79 805-809
  - isoniazid-isoniazid in, (Notes) 67 674-675
  - isoniazid-streptomycin singly and together in, (Notes) 72 846-850
- kanamycin, streptovaricin, paromomycin, novobiocin, and ristocetin in, (Notes) 79 673-676
- macrocydon in, (correspondence) 76 915-916
- Triton WR 1339 in, (correspondence) 76 915-916

**Lesion(s)**

- basal, in chronic emphysema, 68 24-30
- chest
  - asymptomatic and circumscribed, 62 512-517
  - undetected in mass roentgenographic survey, 64 249-255
- coalescent, of diatomaceous earth pneumoconiosis, 77 644-667
- "coin," of lung, (Notes) 73 134-138
- necrotic, tubercle bacilli in, biology of, (Notes) 66 629-631

*Lepra*(s) and

## pulmonary

with atypical acid fast bacilli in sputum, 75 199-222

in BCG vaccinated and unvaccinated persons, 68 695-712

correlation with tuberculin reaction in BCG-vaccinated and control persons, 68 713-726

diffuse, roentgenograms of, (correspondence) 60 536-538

due to *Crotylococcus neoformans*, (case reports) 71 141-144

importance of tuberculin test in differential diagnosis of, 63 110-119

isoniazid effect on growth of tubercle bacilli in, (Notes) 79 518-521

## tuberculous

amithio-one in, 65 692-708

bacteriology of, 71 376-387

pathologic study of, 71 (Supplement, March 1-214)

## resected

bacteriology of, 66 36-43

clinical and bacteriologic correlation of, 70 689-701

culture of *M. tuberculosis* from, comparison of bovine albumin and physiologic saline, (Notes) 70 370-372

late emergence of *M. tuberculosis* in cultures of, 70 191-218

*M. tuberculosis* in, 77 215-259

from patients treated with streptomycin-PAS, cultural properties of *M. tuberculosis* in, 68 727-733

tubercle bacillus in, 66 44-51

spread of, as result of thoracoplasty, 61 648-661

residual, post treatment resection of, 73 165-190

results of thoracoplasty in relation to type of, 60 273-287

segmental, in primary tuberculosis in childhood, 79 756-763

## tuberculous

bacteriologic problems of, 80 (Supplement, October 47-71)

bronchial, intra- and extraluminal, 74 (Supplement, August 256-266)

bronchoscopy in, (Notes) 73 586-588

chronic, in guinea pigs, streptomycin in, 66 191-212

effect of streptomycin on morphology of, 61 525-542

## healing

anatomic changes in, (Notes) 72 386-389

pathology of, 80 (Supplement, October 47-71)

pathology and bacteriology of, 74 (Supplement, August 13-21)

quartz dust for challenging viability of tubercle bacilli in, (Notes) 69 841-842

produced by isoniazid-resistant tubercle bacilli, regression of, (Notes) 70 531-532

relapse of, during and after chemotherapy, duration of drug treatment in, 80 (Supplement, October 47-71)

survival of bacilli in, (Notes) 65 637-640

vascular, in tuberculous meningitis, 61 247-256

Leukemia  
infiltration causing alveolar capillary block, (case reports) 80 895-901

with miliary-meningeal tuberculosis, (case reports) 70 509-517

pulmonary involvement in, 80 833-844

## Leukocyte(s)

from BCG-vaccinated guinea pigs, sonic fragility in, 79 323-328

blood, in tuberculin sensitivity, 78 346-352

## cytolysis

"plasma factor" in, (Notes) 79 244-245

test, 63 672-673

*in vitro* by tuberculin, 60 212-222

human, sensitivity to OT, 75 807-822

lysis, related to tuberculous serology, 69 1002-1015

migration, inhibition of, specific and nonspecific, 80 19-25

in tissue cultures of normal and tuberculous animals affected by tuberculin fractions, 65 250-271

Leukopenia, 59 311-316

Liberia, school-age children of, tuberculin patch-test survey in, (Notes) 67 665-668

Life-table method, in studies of outcome of chronic disease, (editorials) 63 608-612

Ligation, suture, and partial thoracoplasty, in pulmonary tuberculosis, 70 61-70

Light, effect on PAS assay, 75 93-98

## Lipid(s)

extraction, biologic properties of mycobacteria after, 79 296-306

mycobacterial, isoniazid effect on, 72 713-717

of rabbit tissue, in experimental tuberculosis, 75 83-92

toxic, of tubercle bacillus ("cord factor")

isolation of, from petroleum ether, extracts of young bacterial cultures, 67 629-643

## occurrence

in chloroform extracts of young and older bacterial cultures, 67 828-852

in various bacterial extracts, 67 853-858

of tubercle bacilli, living and killed, 66 28-35

- Liver**  
 damage  
   in pulmonary tuberculosis, 72 71-90  
   by pyrazinamide, serum enzymes in, 80 855-865  
 derangement, in pulmonary tuberculosis, 76 410-425  
 effect of pneumoperitoneum on, 65 589-595  
 fatty, production in rabbits by hydrazine derivatives, (Notes) 73 956-959  
 peliosis, (case reports) 67 385-390  
 toxicity of pyrazinamide-isoniazid in tuberculosis, 80 371-387  
   in tuberculosis, clinical, functional, and needle biopsy study of, 63 202-209
- Lobar ventilation** *See* Ventilation
- Lobe(s)**  
 anomalous tracheal bronchus to the right upper, (case reports) 64 686-690  
 lower  
   artificial pneumothorax in, 59 50-52  
   disease in pulmonary tuberculosis, 60 15-24  
   pulmonary tuberculosis in, 59 39-49  
   tuberculous cavities in, 63 625-643  
 middle  
   syndrome, 71 775-784  
   traction diverticula of esophagus in, 65 455-464
- Lobectomy**  
 bronchspirometry before and after, 75 710-723  
 in esophagobronchial fistula associated with severe hemorrhages, (case reports) 63 220-226  
 intrapulmonary gas mixing in, 78 1-7
- Löffler's pneumonitis** *See* Pneumonitis
- Löffler's syndrome**, 59 679-686, (case reports) 63 480-486  
   in connection with PAS allergy, 65 235-249, (case reports) 70 171-175
- Los Angeles County (California)**  
 mass screening program in jail, 74 590-596  
 Hospital, routine roentgenography on admission to, 69 940-956
- Lucite plombage** *See* Plombage
- Lung(s)**  
 abscess  
   acute, 61 474-482, 69 673-681  
   in tularemia, (case reports) 65 627-630  
 anatomy  
   microscopic, 80 (Supplement, July 24-40)  
 apex, pulmonary tuberculosis confined to, 63 644-656  
 arterial circulation of, agenesis in, (case reports) 79 641-651  
 beryllium granulomatosis in, 74 533-540  
 biopsy, 71 668-675  
   in pulmonary actinomycosis, (case reports) 76 660-668  
   bullae, function after excision, 77 387-399  
   cancer, 70 763-783  
   carcinoma, primary, of, with tuberculosis, 79 134-141  
   cavitation in periarthritis nodosa, (case reports) 74 624-632  
   circulation *See also* Pulmonary function  
   capillary, 71 822-829  
   and gas exchange, influence of ventilatory mechanics on, 80 53-58  
   "coin" lesions, (Notes) 73 134-138  
   collagen and elastin of, 80 (Supplement, July 45-48)  
 cysts  
   air, giant, surgical management of, (case reports) 63 579-586  
   infected by *M. tuberculosis*, (case reports) 69 1037-1041  
 decortication, in pulmonary tuberculosis, 59 30-38  
 density, as measure of mouse tuberculosis, 77 681-693  
 diffusing capacity *See* Pulmonary function  
 disease  
   alveolar-arterial oxygen tension gradient in, 69 71-77  
   atypical  
   chromogenic mycobacteria in, 75 180-198  
   mycobacterial, 75 199-222  
   from atypical tubercle bacilli, (case reports) 80 738-743  
   blood flow through nonventilated portions, 68 177-187  
   bronchogenic carcinoma as differential diagnostic problem in, 63 176-193  
 chronic  
   from atypical mycobacterial infections, 80 188-199  
   gross, relationship of allergy to, 78 226-234  
   immunologic aspects of, 79 212-220  
   and respiratory function in tuberculosis (Soviet translation), 79 142-151  
   nontuberculous, incorrectly diagnosed, 75 921-937  
   polyvinyl-formal sponge prosthesis in, 74 581-589  
   rheumatoid, (case reports) 80 732-737  
   tracheal fenestration in, 78 815-821  
 distribution of drug-resistant tubercle bacilli in, 73 406-421  
 elastance, application of Hooke's law to, (Notes) 77 863-866  
 emphysema of  
   chronic, energy cost and control of breathing in, 80 (Supplement, July 131)  
   eosinophilia infiltrating, 59 679-686  
   experimental, 80 (Supplement, July 158-167)

*Lung(s), emphysema of, cont*

- variability of behavior within, 80 (Supplement, July 136)
- and vascular changes, 80 (Supplement, July 67-91)
- fibrosis**
  - carbon monoxide diffusing capacity in, 74 317-342
  - cardiopulmonary function in, 80 700-704
  - diffuse, interstitial, (case reports) 68 603-614, 74 485-510
- function** *See* Pulmonary function
- hemangiopericytoma** of, (case reports) 77 496-500
- histoplasmosis**, diagnosed by scalene node biopsy, (case reports) 66 497-500
- human**
  - preparation for macroscopic and microscopic study, 80 (Supplement, July 114-117)
  - respiratory portion, pre- and postnatal development of, 80 (Supplement, July 5-10)
- immobilizer**, in pulmonary tuberculosis, (correspondence) 66 778-780
- infiltration** *See also* leukemia, below
  - disseminated, nodular, indeterminate in apparently healthy persons, 65 128-141
  - with histoplasmin sensitivity, 59 636-642
- inflammation**
  - chronic, interstitial, with fibrosis, and bronchiolar carcinoma, 76 559-567
  - nontuberculous, effect on pulmonary tuberculosis, 59 68-75
- inflation** or deflation in respiration regulation, 73 519-528
- insufficiency**
  - chronic, radioactive iodine ( $I^{131}$ ) in, 80 181-187
  - prevention of, after pleurisy, 66 134-150
- in leukemia**
  - infiltration of, causing alveolar-capillary block, (case reports) 80 895-901
  - involvement, 80 833-844
- lymphatics** of, in reference to emphysema, 80 (Supplement, July 50-56)
- malignancy** *See also* Tumors
  - cytologic diagnosis of, 61 60-65
  - and eosinophilia, (case reports) 75 644-647
  - mucormycosis of, (case reports) 79 357-361
  - mycotic diseases of, in India, (Notes) 78 644-646
  - nodules, calcified, in relation to bronchogenic carcinoma, 66 151-160
  - normal, blood flow through nonventilated portions, 68 177-187
  - physical properties of, 80 38-45
  - pneumoperitoneum in, physiologic effects of, 60 706-714
  - pneumothorax in, 64 1-20, 21-26, 27-40, 127-140, 141-150, 151-158
  - post-thoracoplasty, resected, 60 406-418
  - proteinosis, alveolar, of, (case reports) 80 249-254
- resection**
  - bronchial ulceration after, 69 84-91
  - pulmonary function before and after, 72 453-464
  - for pulmonary tuberculosis, bronchial disease in, 68 657-677
- sarcoidosis** of, evolution of, (case reports) 80 71-77
- schistosomiasis** of, chronic, 79 119-133
- specific antibodies, in rabbits, 78 259-267
- specimens**
  - methyl-metacrylate in, 76 789-798
  - occult tuberculous endobronchitis in, 77 931-939
- structure**, in three dimensions after inflation and fume fixation, 79 764-772
- susceptibility** to industrial dusts inhaled, 62 (Supplement, July 13-21)
- suture** in tuberculosis, 70 61-70
- tissue**, viability of tubercle bacillus in, 59 429-437
- trauma** at pneumothorax induction, 60 557-563
- tuberculoma** of, 78 403-410
- tuberculous** *See also* under Tuberculosis
  - focus, primary, of, local reactivation in, 78 547-562
  - gas mixing in, 74 343-350
  - resection**
    - in Hawaii, 80 6-11
    - histologic study of blood vessels in, 64 489-498
  - tumor** *See* Tumors
  - vascular changes, in pulmonary tuberculosis, 75 410-419
  - ventilation, defective, analysis by timed capacity measurements of, 64 256-278
- Lupus erythematosus**
  - cells**
    - in miliary tuberculosis, (case reports) 74 112-116
    - in sarcoidosis, (correspondence) 74 811
  - surgery in, (case reports) 77 338-345
- Lupus vulgaris** cutis, fatality ratio for, 80 659-675
- Lymphadenitis**
  - mesenteric, complication of, (case reports) 65 210-214
  - tuberculous**
    - cervical, X-ray therapy in, (Notes) 74 641-644
    - peripheral, X-ray therapy for, 68 157-161
    - sodium silicolyte in, (correspondence) 68 910-911
    - treated by tuberculin desensitization, (case reports) 60 219-257



- Lymphadenopathy**  
 intrathoracic, transient, in apparently healthy persons, 67 45-58  
 scalene, (Notes) 76 503-505
- Lymphatics**  
 as drainage for parietal and visceral pleura, 79 52-65  
 pulmonary, in reference to emphysema, 80 (Supplement, July 50-56)  
 role in development of bronchogenic tuberculosis, 67 440-452
- Lymph node(s)**  
 causing hemoptysis, removal of, (case reports) 65 206-209  
 giant, hyperplasia of mediastinum, (case reports) 79 232-237  
 hilus, calcified, 60 1-14  
 mediastinal, calcified, 62 213-218  
 regional, calcification of, after BCG vaccination, 73 239-245  
 sarcoid, effect on tubercle bacilli of products of, 61 730-734  
 tuberculous, in children, enzymatic therapy for, 76 588-600  
   complications, 70 610-622  
   hemorrhage from abdominal aorta into jejunum through, (case reports) 65 210-214  
   in neck, axilla, and groin, 73 229-238  
   treatment in accessible nodes, (editorials) 64 691-694
- Lymphosarcoma** *See* Tumors
- Lysis, cellular, in tuberculin sensitivity, 68 746-759**
- Lysozyme(s)**  
 action on mycobacteria, 68 564-574  
 lethal and cytologic effects on tubercle bacilli, 67 217-231  
 tuberculostatic substance in serum with properties like, 64 669-674
- Lytic factor, against *M. tuberculosis*, (Notes) 72 859-862**
- M**
- Macacus irus*** *See* Monkeys
- Macrocydon, in murine leprosy, (correspondence) 76 915-916**
- Madison sentence-completion form, (Notes) 74 964-967**
- Malachite green**  
 effect on growth of *M. tuberculosis*, 74 50-58  
 and Triton WR 1339, in charcoal media for tubercle bacilli, (Notes) 71 894-897
- Malignancy(ies)** *See also* Cancer, Tumors  
 pulmonary, cytologic diagnosis of, 61 60-65
- Marine Corps, tuberculin testing in, 62 518-524**
- Marsilid®** *See* Iproniazid
- Maryland, University of, tuberculosis in medical students at, 79 746-755**
- Masks, gauze, efficiency of, 59 1-9**
- Maximal breathing capacity** *See also* Pulmonary function  
 in obese subjects, (Notes) 80 902-903  
 spirometric and Douglas Bag measurement comparisons, (Notes) 79 253-255
- Maximal expiratory flow rate apparatus for bedside and office use, 80 724-731**
- Maximal midexpiratory flow, 72 783-800**
- Measles, and BCG vaccination, (case reports) 72 228-230**
- Media** *See* Medium(a)
- Mediastinum**  
 cysts of, and neoplasms in children, 74 940-953  
 electrocardiogram after, shift to the left in, 64 64-70  
 emphysema of  
   complicating induction of pneumoperitoneum, (case reports) 63 591-596  
   after pneumoperitoneum, (case reports) 68 775-781  
 lymph nodes in  
   calcified, (case reports) 62 213-218  
   hyperplasia of, (case reports) 79 232  
 tuberculoma of, 64 327-352  
 tumors of, 60 419-438  
   cardiospasm simulating, (case reports) 63 597-602
- Medical schools, teaching of tuberculosis in, (editorials) 60 140-142**
- Medical students, tuberculosis in, at University of Maryland, 79 746-755**
- Medium(a)**  
 agar, transparent, growth and enumeration of mycobacteria in, 64 81-86  
 artificial, used for detection of small numbers of tubercle bacilli from dispersed cultures, 65 572-588  
 chick embryo compared with ATS medium in isolation of tubercle bacilli, (Notes) 76 703-705  
 contrast, water-soluble, in bronchography, 68 760-770  
 culture  
   artificial, isolation of *M. tuberculosis* on, (Notes) 70 912-915  
   charcoal  
     for *M. tuberculosis*, 71 382-389  
     drug susceptibilities, (Notes) 71 447-451  
     for tubercle bacilli, 70 955-976  
     Triton WR 1339 and malachite green in, (Notes) 71 894-897  
   for *M. tuberculosis*, blood bank blood agar, (Notes) 71 762-764  
   for tubercle bacilli, for diagnosis, 63 459-469  
   comparison of several media, 63 470-475

*Medium(a), cont***Dubos**

- inactivating isoniazid, (Notes) 68 284-285
- with penicillin
- instability of, (Notes) 80 262-263
- for isolation of *M. tuberculosis* from human discharges, (Notes) 64 318-321

**egg**

- egg laid, elimination of precleaning, (Notes) 79 677
- cultivation of tubercle bacilli, (Notes) 73 139-141

**egg-yolk, for tubercle bacilli, 70 977-988****glycerol blood agar, response of acid fast chromogenic bacilli, 72 119-122****liquid, growth of *M. tuberculosis* in, 73 716-725****liquid and solid, for detection of streptomycin resistance in *M. tuberculosis*, 62 101-108****relationship to growth, morphology, and virulence of *M. tuberculosis* var *avium*, 66 567-577****semisynthetic, autoclavable, in tuberculosis laboratory, (Notes) 78 788-792****solid, for testing streptomycin susceptibility, 62 484-490****synthetic, liquid, new, for cultivation of *Mycobacterium* species, (Notes) 80 267-268****Triton malachite green-charcoal agar, (Notes) 75 338-339****Mega esophagus See Achalasia****Meningeal tuberculosis See Tuberculosis, meningeal****Meningitis****bacterial, streptokinase-streptodornase in, 71 12-29****cryptococcal and tuberculous, in reticulum cell sarcoma, (case reports) 78 760-768****with miliary tuberculosis and leukemia, (case reports) 70 509-517****pneumococcal, combined with tuberculous, (case reports) 71 584****pyogenic, with tuberculous meningitis, (case reports) 62 441-445****serous intracranial, calcification after, (case reports) 78 101-105****tuberculous, (correspondence) 78 485****in adults, 74 830-834****streptomycin-treated, 67 613-628****antimicrobial drugs in, 69 192-204****in children, 76 832-851****combined with pneumococcal, (case reports) 71 584-591****corticotropin in, (case reports) 72 825-832****cortisone in, (case reports) 73 99-109****after cortisone therapy, 64 564-571****discussion, (Notes) 65 637-640****effect of induced hyperglycemia on glucose content of cerebrospinal fluid in, 67 59-73****experimental, isoniazid, iproniazid, streptomycin, and isoniazid-streptomycin in, 70 714-727****fatal, during isoniazid-streptomycin therapy, (case reports) 72 653-658****in guinea pigs, produced by lumbar intrathecal inoculation, 66 722-731****intracranial calcification after, 78 38-61****isoniazid in, deleterious effect possible, (correspondence) 71 765-766****during isoniazid therapy, (case reports) 73 940-943, (correspondence) 74 480****neomycin failure as adjuvant to streptomycin, (case reports) 65 325-331****neoplastic disease simulating, (case reports) 69 1029-1036****pathogenesis of, 64 408-418****pathology of, 61 171-184, 64 419-429****pneumoencephalography in, 74 835-855****during pregnancy, (case reports) 76 1079-1087****prognosis of, 65 168-180****and treatment, 80 388-397****with pyogenic meningitis, (case reports) 62 441-445****reaction to PAS simulating, (case reports) 64 682-685****with spontaneous recovery, (case reports) 72 231-235****streptodornase-streptokinase in, 71 12-29****streptomycin therapy in, 61 171-184, 62 586-593****therapy, specific, for, (editorials) 61 263-268****treatment of, 69 370-382, 74 (Supplement, August 221-224)****results in 549 patients, 69 13-25****tuberculin in, (case reports) 74 277-283****vascular lesions in, (case reports) 61 247-256*****in vitro* susceptibility of tubercle bacilli in, 74 (Supplement, August 232-240)****Mental patients****tuberculosis morbidity and mortality among, 70 32-48****tuberculous, reserpine in, (Notes) 74 457-461****Mesenchyma, extrapleural, (case reports) 75 638-643****Mesothelioma See Tumors****Metabolism****bacillary, effect of isoniazid on, 80 404-409****carbohydrate, associated with amithuozone, (case reports) 66 373-377****nitrogen, in nontuberculous patients receiving isoniazid, 68 207-211****of tubercle bacillus, production of a pharmacologically active metabolite, 63 100-107**

- Metabohte(s)  
 of *M. tuberculosis* H37Rv and H37Ra, differential response to, (correspondence) 62 333  
 neutralization by, of isoniazid activity, 73 735-747
- Methanol extracts  
 of tubercle bacilli, (correspondence) 74 807-808  
 immunizing effect on mice, (Notes) 73 781-784
- Methemoglobin, and hemoglobin values in tuberculous patients on isoniazid therapy, (Notes) 68 286-289
- Methemoglobinemia following treatment with PAS, (case reports) 76 862-866
- Methylene blue reduction time of serum, tuberculosis influence on, (Notes) 70 907-909
- Methyl-metacrylate, in lung specimens, 76 789-798
- Mice  
 antituberculosis chemotherapeutic activity in, 64 541  
 antituberculosis immunity and nutrition in, 77 93-105  
 brains, *Mycobacterium X* in, 71 88-96  
 lesions of, 71 97-111  
 immunity, sex differences in, 75 618-623  
 infection with tubercle bacilli, relation between dosage and survival time, 64 534-540  
 intravenously infected, isolation of tubercle bacilli from feces and gastric contents, 62 481-483  
 nonpathogenic, viable tubercle bacilli in, 75 280-294  
 PAS-streptomycin therapy in, 62 156-159  
 thioureas, substituted, in tuberculosis in, 70 121-129  
 Triton A-20 in antituberculosis activity in, 65 718-721  
 tubercle bacilli in  
   small numbers detected in dispersed cultures, 65 572-588  
   virulent, detected when coexisting with attenuated bacilli, 70 1053-1063  
 in tuberculosis, experimental  
   antagonism of isoniazid-streptomycin in, (Notes) 68 277-279  
   controlled with intermittent streptomycin, viomycin, isoniazid, and streptomycin-diene isonicotinyl hydrazine, (Notes) 68 292-294  
   isoniazid in, 65 357-364, 376-391, 392-401  
   combined chemotherapy with, 68 411-418  
   pyrazinamide in, 65 511-518  
 tuberculous  
   BCG in, 68 451-454  
   tuberculin shock in, (Notes), 68 629-630  
   vaccination with BCG, *n*-hexadecane as adjuvant, 75 624-629
- Microbial persistence modified by isoniazid, (Notes) 76 1106-1109
- Micrococcus pyogenes* var *aureus*, sensitization of guinea pigs to, in presence of "wax" of acid-fast bacilli, 69 241-246
- Microculture, in blood of tubercle bacilli in pathologic specimens, (correspondence) 73 785-786
- Microculture method for isolation of tubercle bacilli, (Notes) 75 1007-1008
- Microolithiasis, pulmonary alveolar, (case reports) 75 122-134
- Microorganism(s)  
 acid-fast  
   growth characteristics of, (Notes) 80 744-746  
   procedure for differentiating between, 76 468-479  
 viomycin activity against, *in vitro* and *in vivo*, 63 17-24
- Microradiography, in emphysema, 80 (Supplement, July 104-112)
- Microscopy  
 and culture of *M. tuberculosis*, in BCG vaccinated mice, 79 484-491  
 electron  
   effect of PAS-isoniazid-viomycin on tubercle bacilli, (Notes) 73 296-300  
   in study of mycobacteriophages, 76 964-969  
   of tubercle bacilli, streptomycin-treated, 70 328-333  
 fluorescence, of *M. tuberculosis*, 65 709-717  
 of *M. tuberculosis*, from sputum of isoniazid-treated patients, 70 349-359  
 phase contrast, of corneal tuberculosis, 74 1-6  
 Middle age, resection in, 73 40-51
- Middlebrook-Dubos hemagglutination test *See* Hemagglutination
- Middlebrook-Dubos titer, and serum protein electrophoretic pattern in BCG-vaccinated tuberculous children, (Notes) 79 522-524
- Middle lobe syndrome, roentgen therapy in, (case reports) 76 291-297
- Miliary tuberculosis *See* Tuberculosis, miliary
- Military personnel of World War II, pulmonary tuberculosis in, 75 1-40
- Military tuberculosis hospital, histoplasmosis in, (Notes) 75 833-835
- Miners, coal *See* Pneumoconioses, anthracite
- "Minimal," sopulstry in use of the word, (correspondence) 79 681
- Minimal tuberculosis *See* Tuberculosis, minimal
- Mitochondria, and nuclei in *M. tuberculosis*, 67 59-73
- Monaldi procedure, 65 83-87
- Moniliasis *See* Mycoses

## Monkey(s)

- effect of alteration of pulmonary arterial circulation on tuberculosis in, 65 48-63
- isoniazid toxicity for, (correspondence) 68 470
- Macaca mulatta*, antituberculosis therapy in, 76 225-231

*Macacus irus*, *H. capsulatum* in, (Notes) 75 849-851

## rhesus

- isoniazid toxicity for, 67 798-807
- pathogenicity of atypical chromogenic bacteria for, 75 169-179

tuberculosis in, 72 204-209

Monocytes, immunity studies with, 79 221-231

Mononucleosis, infectious, simulated by PAS reaction, (case reports) 72 833-839

## Morbidity

- rates, in tuberculosis, 61 39-50
- in household associates, 65 111-127

## tuberculosis

- among mental patients and general population, 70 32-48
- related to tuberculin sensitivity and body build, 76 517-539
- trend, 67 279-285

Morphology of fatal tuberculosis in childhood, 74 (Supplement, August 7-12)

## Mortality

- rates, in tuberculosis, 61 39-50
- in household associates, 65 111-127

## tuberculosis

- among mental patients and in general population, 70 32-48
- among residents of large cities (1947-1949), 66 109-116

Mouse *See* Mice

Mouth wash, detection of tubercle bacilli in, 71 371-381

Mucin, hog gastric, in experimental tuberculosis, (Notes) 77 1005-1011

Mucoid impaction of the bronchi, 76 970-982

Mucoproteins in pleural effusions, 76 247-255

Mucormycosis *See* Mycoses

Mucosa, bronchial, regenerative versus atypical changes in, 79 591

Multiple sclerosis, isoniazid in, 70 577-592

Murmur, millwheel, presumably caused by air embolism in pneumoperitoneum, (case reports) 70 1092-1095

Myasthenia gravis, with malignant thymoma, (case reports) 72 381-385

## Mycobacteria

- affected by Su 1906, Su 3068, and Su 3912, 77 694-702

amithiozone resistance and action in, mechanism of, 80 559-568

arithmetic linear growth of, 66 756-761

asparaginase of, (Notes) 70 920-921

## atypical

- antimicrobial effect on, 78 454-461
- characterization by microcolonial test, 76 451-467

comparative pathogenicity of, in experimental animals, 80 876-885

in HeLa cells, 77 968-975

infections from chronic pulmonary disease from, 80 188-199

## isolation of

- from healthy persons, (Notes) 80 747-749
- and *Nocardia*, 76 451-467, 468-479

niacin production of, 77 669-674, 675-680

## atypical chromogenic

fluid thioglycollate medium in, (Notes) 77 356-358

pathogenicity of, for rhesus monkey, 75 169-179

in pulmonary disease, 75 180-198

avirulent, metabolism of, 66 416-435

biologic properties after lipid extraction, 79 296-306

carbolfuchsin stained, in diagnostic films, 74 597-607

catalase enzyme of, 77 146-154

in cell and tissue cultures, 77 789-801

cells, crude, biologic activity of, (Notes) 80 274-276

in chick embryo, influenced by temperature, 73 650-673

from cold blooded animals, 77 823-838

communion by ultrasonic exposure, (correspondence) 76 914-915

comparison between atypical and selected strains, (Notes) 76 497-502

cooperative study, (correspondence) 72 866-870

cord formation and virulence, 78 83-92

cording and cytochemical reaction, 73 674-680

enzymatic characteristics of suspensions of, (correspondence) 61 270-271

extracts in inactivation of isoniazid, 72 196-203

filtration, from organic solvents, 77 290-300

fluorescence microscopy in detection of, in tissue sections, 68 82-95

in fowl embryos, 73 276-290

genetics of, detection of small numbers of virulent tubercle bacilli when coexisting with attenuated bacilli in the mouse, 70 1053-1063

## growth of

- and enumeration, in transparent agar medium, 64 81-86

oxygenation and aeration effect on, 70 665-671

rates, in biochemical studies, (Notes) 79 94-96

infection, mycobacterial, heterologous and homologous immunity in, 76 76-89

lysozyme action on, 68 564-574

*Mycobacteria, cont*

- and mammalian cells in tissue culture, (correspondence) 75 347-348
- metabolism, relationship of isoniazid to, 75 62-70
- in mice, influenced by temperature, 73 650-673
- neomycin activity on, 60 78-89
- neutral red reactions on, (Notes) 79 526-530
- niacin test in distinguishing, (Notes) 79 663-665
- nonpathogenic, as source of error in diagnosis and drug-susceptibility tests, 68 557-563
- oxidation-reduction dyes in determining virulence, *in vitro*, 65 187-193
- paratubercle bacilli, skin reaction to products of, 79 731-737
- photochromogenic, infections with, chemotherapy and pathology, 80 522-534
- precipitins of, agar diffusion, 73 637-649
- preservation of, by desiccation *in vacuo*, 60 621-627
- purine enzymes in, (Notes) 66 240-243
- resistance to hydrazines of isonicotinic acid, (Notes) 65 754-774
- saprophytic
  - fluid thioglycollate medium, (Notes) 77 356-358
  - and tubercle bacilli, differentiation of, (Notes) 74 948-960
- species, new synthetic liquid medium for cultivation of, (Notes) 80 267-268
- in tissues, retention and differentiation of, 74 608-615
- typical, niacin production of, 77 669-674, 675-680
- virulence of
  - effect of ammonium ions on ability of, to bind neutral red, (correspondence) 60 384
  - metabolism, 66 416-435
  - oxidation-reduction dyes for determination of, (correspondence) 66 382-383, 68 786-787
- in vitro*
  - modification of oxidation-reduction dye test for determination of virulence of, (Notes) 66 99, 69 599-603
- Mycobacteriaceae*, urease activity in, (Notes) 65 779-782
- Mycobacteriophage(s)*
  - biologic properties of, 80 543-553
  - D-29, inhibition of, with human tubercle bacilli, by serum factor, 80 12-18
  - electron microscopic studies of, 76 964-969
- Mycobacterium*
  - avium*
    - drug resistance relationship to growth phase, (Notes) 76 298-300
    - isoniazid-resistant, (Notes) 77 519-523
    - relationship of medium to growth, morphology, and virulence, 66 567-577
    - sulfathiazole resistant, in prevention of streptomycin resistance, (Notes) 76 301-307
  - balnei*, in mice, immunity, heterologous and homologous, 76 76-89
  - butyricum*, temperate bacteriophage from, 80 232-239
  - fortuitum*, 72 53-63
    - bacteriology and pathogenicity for laboratory animals, 76 108-122
  - leprae*, separation from tissues by enzyme digestion, (Notes) 74 152
  - leprae murium*, microbial population counts with anti-leprosy drugs, 69 173-191
  - paratuberculosis*
    - chemical constituents of, (Notes) 77 712-715
    - susceptible and resistant to isoniazid and hydrogen peroxide, differential uptake of isoniazid-C<sup>14</sup> by, (correspondence) 80 110-111
  - phlei*, specificities of aqueous and saline extracts, 73 563-570, 571-575
  - ranae*, cross-resistance to 28 antimycobacterial agents, 69 267-279
  - isoniazid-dependent strains, (Notes) 68 631-633
  - neomycin and dihydrostreptomycin resistance in, 62 286-299
- smegmatis*
  - metabolizing glucose, (Notes) 73 589-592
  - stained with indicator dyes, phagocytosis of, 74 552-565
  - streptomycin inhibiting growth of, 71 743-751
- tuberculosis* See also Tubercle bacilli
  - action of cycloserine on, *in vitro*, (Notes) 72 236-241
  - antituberculosis drugs in, combined, (Notes) 78 121-126
  - autolysis, glucose and oxygen in, 73 907-916
  - BCG, metabolism of isoniazid by, (Notes) 78 806-809
  - $\beta$ -propylal- $\gamma$ -butylal-imine inhibiting, (Notes) 76 1094-1096
  - bovine, in experimental tuberculosis, 68 220-228
  - catalase activity, 78 735-748
  - chick yolk sac technique in, (Notes) 77 511-515
  - constituents, 61 798-808
  - correlation of biologic properties with infrared spectrums, 65 477-480
  - cultural properties, in resected pulmonary lesions of patients treated with streptomycin-PAS, 68 727-733

## Mycobacterium tuberculosis

## culture

- chamber method (Notes) 72 393-397
- charcoal, 71 382-389
- colorimetric catalase test in, (Notes) 71 305-307
- compared with mouse and guinea pig inoculation, 69 92-103
- comparison of laryngeal swabs and gastric aspiration for, 67 598-603
- comparison of tracheal and gastric lavage in 68 926-932
- medium for, blood bank blood agar, (Notes) 71 762-764 *See also* Medium(a)
- method, (Notes) 69 304-306
- negative, procedure with, (correspondence) 69 128
- obtained by incubation beyond the normal 7- or 8 week period, (Notes) 69 307-308
- preservation by freezing, 62 99-100
- purified tuberculin fraction from, (Notes) 69 300-303
- from resected lesions, comparison of bovine albumin and physiologic saline in, (Notes) 70 370-372
- by slide culture method, 72 330-339
- sputum for, obtained during local anesthesia, (Notes) 74 977
- urine, during chemotherapy, 70 149-154
- dissociation, 62 (Supplement, July 22-33)
- drug susceptibilities, (Notes) 71 117-151
- rapid method for determination, (Notes) 78 111-116
- results of *in vitro* test for, 63 679-693
- enzymatic reactions of, and action of streptomycin, 65 722-731
- filterable forms, (correspondence) 69 473-474
- fluid thioglycollate medium in, (Notes) 77 356-358
- fluorescence microscopy in, 65 709-717
- generation time on solid and liquid media, 74 50-58
- growth
  - delayed, from resected lung specimens, (correspondence) 71 319
  - in liquid media, 73 716-725
  - measurement, 62 87-90
  - from resected specimens under various atmospheric conditions, (Notes) 70 910-911
- H37Ra strain, mechanical agitation in growth of, (Notes) 79 813-815
- H37Rv strain
  - activity of antituberculosis drugs, 59 461-465
  - catalase activity, (Notes) 80 257-258

- development of atypical variants *in vitro* with isoniazid-streptomycin, (Notes) 78 921-926
- leukocytic susceptibility to tuberculin in guinea pigs infected with, (Notes) 76 888-891
- mutant, protein precipitated by, (correspondence) 77 1031-1032
- specificities of aqueous and saline extracts, 73 563-570
- in HeLa cells, 77 123-135
- infection in mice, 73 251-265
- infrared spectrums of, 63 372-380, 69 505-510
- isolation of
  - on artificial media and embryonated eggs, (Notes) 70 912-914
  - in egg yolk media, (Notes) 72 863-865
  - from human discharges, use of Dubos type medium containing penicillin, (Notes) 64 318-321
- microculture technique, (Notes) 73 576-580
- and isoniazid
  - action within phagocytes, (Notes) 65 775-776
  - activity in, neutralized by metabolites, 73 735-747
  - inhibition by pyridoxal, 76 568-578
  - resistance, 70 442-452
    - hemin as growth factor for, 69 797-805
    - peroxide formation in media for, 75 476-487
  - strains, virulence of, 71 799-809
  - susceptible and -resistant strains, catalase and peroxidase activities, (Notes) 79 669-671
- kanamycin in, (Notes) 78 138-139
- lack of significant *in vitro* susceptibility to pyrazinamide on solid media, (Notes) 67 391-395
- late emergence in cultures of resected lesions, 70 191-218
- lipids, infrared spectroscopic examination of, 73 529-538
- lung cyst infected by, (case reports) 69 1037-1041
- lytic factor against, (Notes) 72 859-862
- medium(a) *See* Medium(a)
- metabolism, isoniazid effect on, 80 404-409
- metabolites, differential response to, (correspondence) 62 333
- neomycin activity, 60 78-89
- nuclei and mitochondria in, 67 59-73
- PAS resistant, (Notes) 77 346-349
- persistence, in drug-treated animals, 77 473-481
- photosensitivity, 71 112-125
- "plasma factor" in leukocyte cytolysis in

*Mycobacterium, tuberculosis cont*

- guinea pigs sensitized with, (Notes)  
79 244-245
- preservation of cultures by freezing, (Notes)  
64 696-697
- protein fraction, 66 314-334
- in relation to *B abortus*, (correspondence)  
74 478
- in resected lesions, 77 245-259
- resistance
  - to drugs, 61 483-507
  - of monocytes to, 77 436-449
  - to streptomycin
    - in children, 66 63-76
    - medium for detection, 62 101-108
- resistant strain, effect of Triton A-20 and  
pH on streptomycin susceptibility  
of, 62 91-98
- self-inoculation by a diabetic woman with,  
(case reports) 69 818-823
- sexual cycle, possibility of, (correspondence)  
63 721
- slide culture method for detection, 60 51-61
- in sputum, detected by pepsin digestion and  
interface concentration with pen-  
tane, (Notes) 75 148-152
- stained with indicator dyes, phagocytosis,  
74 552-565
- streptomycin
  - dependent strains, (correspondence) 59  
219-220
  - resistant, 59 438-448
  - susceptibility to, 61 705-718
    - effect of Triton A-20 and pH on, 62 91-98
    - plate method for determining, 61 578-581
    - in vitro*, 59 336-352
- sunlamp irradiation effect on, 71 112-125
- utilization of asparagine as source of nitrogen  
for growth, 68 127-135
- vaccines from gamma-irradiated, and from  
*Brucella suis*, (Notes) 79 374-377
- Vallée, isoniazid-resistant mutant, immuniz-  
ing properties of, as compared with  
BCG, (Notes) 70 527-530
- viability of
  - in embalmed human lung tissue, 59 429-437
  - in isoniazid, 69 1022-1028
  - in isoniazid-treated lesions, 70 102-108
- viomycin
  - active against, 63 1-4
  - effect on, *in vitro* and *in vivo*, 63 17-24, 25-29
- virulence
  - in chick embryo, 74 249-257
  - by intracisternal test, 76 426-434
  - microcolonial test for, 71 361-370
- vitamin analogues affecting, 62 (Supplement,  
July 34-47)

- in vivo* and *in vitro* observations on, 74 428-  
437
- in vitro*, trypsin effect on, 76 279-285
- Zephiran® in isolation of, (Notes) 74 284-  
288

*tuberculosis 607*

- effect of nitrogen on growth, riboflavin pro-  
duction and synthesis of a pharma-  
cologically active metabolite, 68  
119-126
- metabolism, 71 260-265
- ulcerans*
  - infections, chemotherapy in, 75 266-279
  - in mice, heterologous and homologous im-  
munity in, 76 76-89

## X

- infectivity and immunogenicity of, in mice,  
79 47-51
- in mouse brains, lesions of, 71 88-96
- Mycoses *See also* Fungi and Fungal antigens
- actinomycosis
  - chemotherapy in, 63 441-448
  - pulmonary, diagnosed by lung biopsy, (case  
reports) 76 660-668
- aerosol amphotericin B in, (Notes) 80 441-442
- blastomycosis, systemic, and chemotherapy  
in pulmonary tuberculosis, (case  
reports) 68 615-621
- coccidioidal cavity, recurrence after resectional  
surgery, (case reports) 71 131-136
- coccidioidal granuloma, acute, disseminated,  
(case reports) 63 476-479
- coccidioidomycosis, 73 501-518
  - acute disseminated coccidioidal granuloma,  
(case reports) 63 476-479
- contagiousness, 61 95-115, (correspondence)  
441
  - in contacts, 59 632-642
  - infection in guinea pigs by contact with dis-  
eased animals, 61 106-115
  - spherules in sputum exposed out of doors,  
61 95-105
- disseminated, 75 828-832
  - and tuberculosis, 59 415-428
- experimental, nystatin in, 72 64-70
- pulmonary, (correspondence) 61 158
  - coccidioidin skin reaction, (case reports)  
79 78
  - coexistent with tuberculosis, 67 477-489
  - with lymphosarcoma and alveolar-capillary  
block, (case reports) 78 463-473
  - surgery in, complications, 77 17-21
- and tuberculosis
  - concomitant, (case reports) 61 887-891
  - pulmonary, 70 109-120
- cryptococcal and tuberculous meningitis com-  
plicating reticulum cell carcinoma,  
(case reports) 78 760-763

## Mycosis

- cryptococcosis, pulmonary, (case reports) 69 116-120
- fungal disease existing with pulmonary tuberculosis, (case reports) 72 667-674
- geotrichosis, pulmonary (case reports) 76 289-290
- histoplasmosis, (case reports) 67 376-381, 77 719-723
  - acute, benign, (case reports) 69 625-630
  - with Addison's disease and pulmonary tuberculosis, (case reports) 72 675-684
  - causing bronchiolithiasis, (case reports) 77 162-167
- cavitary
  - chronic, progressive, clinical aids in diagnosis, 75 935-948
  - progressive, in tuberculosis hospitals, 73 609-619
- chronic, 72 274-296
- communicability of, 63 535-546
- diagnostic aids in, (case reports) 70 360-362
- epidemics, 68 307-320
- lung nodules in, surgical significance of, (case reports) 69 829-836
- in military tuberculosis hospital, (Notes) 75 833-835
- prevalence, histoplasmin conversion rate as indication of, 69 234-240
- pulmonary, 67 453-476
  - chronic
    - chemotherapy in, 75 912-920
    - in pregnancy, with spontaneous pneumothorax, (case reports) 75 111-121
    - diagnosed by scalene node biopsy, (case reports) 66 497-500
  - pulmonary cavitation due to, (case reports) 69 111-115
  - roentgenographic patterns in, 76 173-194
  - small outbreak, 78 576-582
  - vena caval obstruction by, (case reports) 77 848-857
- moniliasis, pulmonary, (case reports) 77 329-337
- mucormycosis, pulmonary, (case reports) 79 357-361
  - laboratory diagnosis of, 61 690-704
- nocardiosis
  - chemotherapy for, 63 441-448
  - pulmonary, 73 485-500
- Mycostatin<sup>o</sup> See Nystatin
- Myocardium, tuberculosis of, (case reports) 74 99-105
  - heart block change in, (case reports) 65 332-338
- Myvisone See Amithiozone, Thiosemicarbazone(s)

## N

- National Tuberculosis Association, fiftieth anniversary, (editorials) 69 631-633
- Navajos, tuberculosis among, (editorials) 61 586, 591, 80 200-206
- Navy
  - streptomycin regimen study in, July 1946-April 1949, 60 715-751
  - tuberculin testing in, 62 518-524
- Necrosis
  - of basal nuclei, in thrombosis of cerebral vessels, (case reports) 61 247-256
  - caseous, protein and nucleic acid in, 77 106-119
- Needle biopsy See Biopsy
- Negro(es)
  - American, tuberculosis control among, 60 332-342
  - tuberculous pneumonia in, 60 343-353, 68 382-392
- Neomycin
  - activity on *M. tuberculosis* and other mycobacteria, 60 78-89
  - aerosol, in pulmonary tuberculosis, (Notes) 78 135-137
  - in clinical tuberculosis, 63 427-433
  - in experimental tuberculosis, 62 300-306, 345-352
  - failure as adjuvant to streptomycin in tuberculous meningitis, (case reports) 65 325-331
  - resistance, genetic studies of, 62 286-299
- Neonatal period, tuberculosis in, 77 418-422
- Neoplasm(s) See Tumors
- Neotetrazolum
  - chloride, in tubercle bacilli cultures, (Notes) 68 625-628
  - inhibition test, 77 662-668
- Nephrectomy, partial, for tuberculosis, 66 744-749
- Nervous system, central
  - isoniazid effect, 69 261-266, 759-762
  - isoniazid-proniazid effects, 69 261-266
- Neuritis, peripheral
  - and isoniazid metabolism, 70 266-273
  - in isoniazid treated patients, (case reports) 70 504-508
- Neuroma See Tumors
- Neuropathy, peripheral, in tuberculous patients treated with isoniazid, (case reports) 68 458-461
- Neurotoxicity, of dihydrostreptomycin
  - effects of longer term therapy, 63 312-324
  - sulfate, 65 612-616
- New York City
  - tuberculosis deaths in, (Notes) 77 516-518
  - tuberculin testing, (Notes) 69 1057-1058



## Niacin

production of typical and atypical mycobacteria, 77 669-674, 675-680

## test

in differentiation of tubercle bacilli, (Notes) 79 810-812

in distinguishing mycobacteria, (Notes) 79 663-665

## Nicotinamide

activation, in acidic environments, *in vitro*, (Notes) 70 748-754

-pyrazinamide, intracellular activation, 74 718-728

therapy of lingual changes in tuberculous patients, 62 360-373

Nicotinic acid, in mycobacteria, metabolism of, 75 529-537

## Nitrogen

asparagine as source of, for growth of *M. tuberculosis*, 68 127-135

clearance, in ventilatory efficiency, 72 465-478

effect, on growth, riboflavin production and synthesis of pharmacologically active metabolite, 68 119-126

influence on antimicrobial activity, 67 503-508

metabolism, in nontuberculous patients receiving isoniazid, 68 207-211

Nitrous fumes, exposure to, 76 398-409

*Nocardia* See Fungi

*Nocardia asteroides* See Fungi

Nocardiosis See Mycoses

Node(s) See Lymph nodes, Scalene nodes

Nodule(s), pulmonary

found in community roentgenographic survey, 79 427-439

in histoplasmosis, surgical significance of, (case reports) 69 829-836

solitary, calcification in, (case reports) 74 106-111

Nontuberculous disease, isoniazid prophylaxis in, (correspondence) 78 485-487

Nontuberculous infections, immunity in, (editorials) 71 592-595

Nose, swab cultures in pulmonary tuberculosis, (Notes) 80 909-910

## NOTES

Actinomycetles, susceptibility to isoniazid, compared with other synthetic and antimicrobial antituberculosis agents, 67 261-264

adenitis, tuberculous, 23 cases treated with isoniazid alone, 74 136-141

adrenocortical hormones in experimental tuberculosis in adrenalectomized mice, 77 536-538

amino acid(s), study of

metabolism, with urine from tuberculous patients, 76 867-870

related to the problem of host resistance to tuberculosis, 66 378-380

amphotericin-B

aerosol, innocuousness and possible therapeutic use, 80 441-442

determination of serum concentrations in man of, 77 1023-1025

antituberculosis drugs, mechanism of the combined effect, 78 121-126

autoclavable medium, semisynthetic, for a routine tuberculosis laboratory, 78 788-792

bacilli, acid-fast

atypical, an expanded schema, 80 434-437

chromogenic

classification and susceptibilities to chemotherapeutic agents, 76 697-702

from human sources, *in vitro* response to a number of antimicrobial agents on glycerol-blood agar medium, 72 119-122

nontuberculous

recovered from human sources, 76 683-691  
studies on, penicillin susceptibility, 75 675-677

wild-type, typical and atypical, titration of cord formation as a measure of pathogenicity of, 78 799-801

bacteriologic specimens, agitator for, 70 176-177

BCG

biologic activity of crude extracts of, 78 939-943

immunization, lack of circulating antibodies after, as assayed by the globulin titration technique, 78 793

and its isoniazid-resistant mutant in guinea pigs, comparative study of the vaccinating properties of, 75 656-658

new method of production, 64 698-701

present status of studies, 68 462-466

vaccination, in Republic of Panama, 67 522-525

vaccine

harvesting and dispensing apparatus for, 63 613-614

new method of counting viable organisms in, 79 816-817

viability, 63 714-716

influence of methods of preparation on, 64 695

vital staining method for the rapid estimation of the bacterial count, 78 785-787

*Notes cont*

- benzoyl para aminosalicylic acid, biochemical aspects of metabolism of, 75 1003-1006
- breathing capacity, maximal, comparison of spirometric and Douglas Bag measurements, 79 253-255
- bronchograms, under hypnosis, 79 525
- bronchoscopy
  - in diagnosis and localization of bacteriologically positive tuberculous lesions, 73 586-588
  - sputum examination after, 77 716-718
- bronchspirometry, vital capacity in, 76 320-321
- calcium benzoyl PAS, 75 667-669
- Candida albicans*
  - and adjuvants, experimental sensitization of guinea pigs with, 76 692-696
  - incidence of, in sputum of tuberculous patients, 72 543-545
  - means for detecting *M. tuberculosis* on culture media, 75 836-840
- case-finding, tuberculosis, in psychiatric hospitals, 79 537-540
- chemotherapeutic compounds, antituberculosis, decomposition of, with reference to susceptibility tests, 73 593-596
- chemotherapy
  - in chronic fibrocaceous pulmonary tuberculosis, relapse rates after, 71 302-304
  - in pulmonary tuberculosis, evaluation of
    - Part I High doses of isoniazid-PAS-pyridoxine, 78 773-778
    - Part II Daily streptomycin plus high doses of isoniazid-PAS-pyridoxine, 78 779-784
  - regimens employing isoniazid alone and in combination with intermittent streptomycin in tuberculosis, incidence of bacterial resistance encountered with, 67 106-107
- chronic bronchitis, some clinical, pathologic, and bacteriologic aspects, 75 340-342
- Coccidioides immitis*, sporulation of 3 strains of, inhibitory effect of peptone on, 74 147-148
- "coin" lesions of the lung, 73 134-138
- corticotropin, effects of decreasing dosages upon the course of ocular tuberculosis in the rabbit, (Notes) 69 1051-1053
- cortisone, effect
  - on electrophoretic patterns and the hemagglutination reaction in the course of childhood tuberculosis, 73 964-965
  - of minimal dose combined with a subeffective dose of dihydrostreptomycin on experimental guinea pig tuberculosis, 67 101-102
- C-reactive protein, in pulmonary tuberculosis, 74 464-467
- cycloserine
  - alone and in combination with other drugs in experimental guinea pig tuberculosis, 75 510-513
  - clinical, bacteriologic, and pharmacologic observations upon, 74 128-135
  - effect
    - on experimental tuberculosis in guinea pigs, 72 117-118
    - on growing and resting tubercle bacilli, 72 685-686
  - evaluation, with high dosage of isoniazid in chronic treatment-failure pulmonary tuberculosis, 80 269-273
  - isoniazid, in ambulatory treatment of active tuberculosis after failure of previous chemotherapy, 80 89-94
  - physiologic disposition of, in experimental animals, 74 802-806
  - psychologic side effects produced by, in treatment of pulmonary tuberculosis, 73 438-441
  - pyrazinamide, in treatment of pulmonary tuberculosis, 78 927-931
  - therapy, in tuberculosis in humans, 74 121-127
  - toxicity
    - considerations of, 75 514-516
    - and pharmacology, 74 972-976
  - viomycin, in treatment of pulmonary tuberculosis, 79 90-93
  - in vitro* action on *M. tuberculosis*, 72 236-241
- cystoscopes, studies on sterilization of, 76 909-911
- 4,4'-diaminodiphenyl sulfone, excretion products of, 72 123-125
- dihydrostreptomycin, purified, 73 776-778
- discharge, length of stay and criteria for, in a large tuberculosis center, 74 961-963
- drug therapy, effect of, upon survival of tuberculous patients, 74 968-971
- electrophoresis
  - serum protein paper patterns
    - and Middlebrook-Dubos titer in tuberculous children after BCG vaccination, 79 522-524
    - preliminary observation with use of, as an index of progress in the tuberculous patient, 76 892-895
    - of tuberculous patients presenting therapeutic problems, 75 999-1002
  - zone, in starch gels, report on Smithies Method in normal adults and in patients with tuberculosis, 78 932-933

## Notes, cont

- emphysema, mediastinal, pathogenesis of, complicating therapeutic pneumoperitoneum, 76 897-898
- empyema, tuberculous, pH of, 67 103-105
- enzymes, use of, to aid filtration of oropharyngeal washes through membrane filter, 79 541
- S-ethyl-L-cysteine, clinical trial in pulmonary tuberculosis, 74 142-144
- ethyl-thio-formyl compound, with antituberculosis activity, 77 1017-1018
- fungi, investigation into the role of, in pulmonary diseases in India, 78 644-646
- glycerol, traces of zinc in, 74 145-146
- HeLa cells, growth characteristics of acid-fast microorganisms other than tubercle bacilli in, 80 744-746
- H<sub>1</sub> Intensity ultraviolet, effect of, for sterilization, 77 457-458
- hinconstarch
- metabolic products of, 74 798-801
- seromucoid (serum mucoprotein) values in patients undergoing therapy by, 78 131-134
- Histoplasma capsulatum*
- and *Blastomyces dermatitidis* polysaccharide skin tests in humans, 80 264-266
- challenge of *Macacus irus* with, 75 849-851
- laboratory infection with, 72 690-692
- Histoplasmin
- sensitivity
- in Alaskan natives, 79 542
- urban focus of, 79 83-86
- Histoplasmin H-42, dose of, for skin testing, 77 546-550
- histoplasmosis, problem of, in a military tuberculosis hospital, 75 833-835
- Hooke's law, application to the elastic properties of the lung of, 77 863-866
- hospital, best doctor in, 79 533-536
- immersion oil, as possible source of diagnostic errors, 63 717
- immunity, antituberculosis, elicited in mice by methanol extracts of tubercle bacilli, enhancing effect of adjuvants on, 73 781-784
- immunization, against tuberculous infection, difference in response of 4 strains of mice to, 80 753-756
- index cards, for clinical data on patients in a tuberculosis hospital, 70 903-906
- infancy, incidence of tuberculous infection in, 74 149-151
- iproniazid, side effects accompanying use of, 68 270-272
- isoniazid
- antagonism of
- by certain metabolites, 68 938-939
- conditional, and other antibacterial agents, 68 280-283
- by hemin, and the tuberculostatic action of, 69 469-470
- antituberculosis action, isonicotinic acid hypothesis of, 77 364-367
- bacteriotropic activity of, in the presence of certain other compounds, 78 802-805
- concentrations
- comparison of, in blood of people of Japanese and European descent, 78 944-948
- in culture media, effect of inspissation and storage on, 75 678-683
- low, reliability of a microbiologic assay technique for measuring, 75 992-994
- cycloserine, report on the use of, in 84 cases of pulmonary tuberculosis, 79 87-89
- effect
- of the "anti-isoniazid" substance produced by mycobacteria on the chemotherapeutic activity *in vivo* of, 73 764-767
- of barbiturates on the toxicity of, 66 100-103
- of early administration on immunizing activity of normal BCG and isoniazid-resistant BCG in guinea pigs, 75 650-655
- on growing and resting tubercle bacilli, 69 125-127
- on growth of tubercle bacilli from pulmonary lesions, 79 518-521
- of ketone compounds by the inhibition of growth of tubercle bacilli *in vitro*, 68 273-276
- on the tuberculin test, 67 535-537
- experiments, on the prophylaxis of a minimal tuberculous infection of guinea pigs with an intermittent regimen, 77 999-1004
- and other hydrazine derivatives, production of fatty livers in rabbits by, 73 956-959
- inactivation of, by Dubos medium, 68 284-285
- ineffectiveness of, in modifying the phenomenon of microbial persistence, 76 1106-1109
- iproniazid, effect on *Coccidioides immitis*, 69 538
- liberation of peroxide in the breakdown of, 73 779-780
- medication, acquired resistance and, 79 97-101

*Notes, isoniazid cont*

metabolism of  
 by *Mycobacterium tuberculosis* BCG, with reference to current theories of the mode of action, 78 806-809  
 use of a serum microbiologic assay technique for estimating patterns of, 75 995-998  
 mode of action of, and role of trace metals in inhibition of bovine liver catalase by isoniazid, studies on, 77 501-505  
 PAS salt of, studies of, in the treatment of tuberculosis, 78 637-643  
 -pyridoxine, massive dose in chronic pulmonary tuberculosis, 78 474-477  
 -resistant cultures isolated from clinical specimens, virulence in guinea pigs of, a preliminary report on, 68 290-291  
 serum concentrations in tuberculous patients, effect of certain aromatic amines on, 76 152-158  
 -streptomycin, antagonism of, in experimental infection of mice with *M tuberculosis* H37Rv, 68 277-279  
 therapy  
   cystlike cavities in pulmonary tuberculosis and, 69 1054-1056  
   experimental reinfection in arrested guinea pig tuberculosis and its behavior under, 79 246-250  
   high dose, further experience with single-drug (isoniazid) therapy in chronic pulmonary tuberculosis, 77 539-542  
   isoniazid serum concentrations and total hemoglobin and methemoglobin values in tuberculous patients on two dosage regimens, 68 286-289  
 Ivalon sponge plombage, 78 478-484  
 kanamycin, effect on *M tuberculosis* *in vitro*, 78 138-139  
 leprosy, murine  
   effects of kanamycin, streptovaricin, paromomycin, novobiocin, and ristocetin on, 79 673-676  
   evolution of, 79 805-809  
 lymphadenopathy, scalene, postmortem study, 76 503-505  
 lymphadenitis, tuberculous, cervical, X-ray therapy in management of, 74 641-644  
 Madison sentence completion form, use in a small tuberculosis sanatorium, 74 961-967  
 mycobacteria  
   asparaginase of, 70 920-921  
   atypical strains  
     drug susceptibilities of 20, as compared

with 19 selected strains of, 76 497-502  
 isolation of, from healthy persons, 80 747-749  
 and others, determination of growth rates as a means of estimating optimal growth periods for comparative biochemical studies, 79 94-96  
 and typical, quantitative aspects of neutral red reactions of, 79 526-530  
 distinguished by the niacin test, 79 663-665  
 effect of glutamic acid derivatives on growth and inhibition of, 75 688-691  
 failure of a method for enzymatic digestion and concentration of pathogenic fungi and, from sputum, 76 896  
 new liquid synthetic medium for the cultivation of species, 80 267-268  
 oxidation-reduction dyes in the determination of virulence of  
   results with, 68 786-787  
   test tube modification of, *in vitro*, 66 99  
 spontaneity of gradual increase of streptomycin resistance in, 75 841-842  
 mycobacterial cells, crude, further observations on the biologic activity of, 80 274-276  
*Mycobacterium avium*  
   genetic consideration on isoniazid-resistance system of, 77 519-523  
   relationship between drug-resistance and growth phase of, 76 298-300  
   sulfathiazole resistant, decrease of mutation rate to streptomycin resistance in produced by presence of sulfathiazole, 76 301-307  
*Mycobacterium leprae*, separation of, from tissues by enzyme digestion, 74 152  
*Mycobacterium paratuberculosis*, chemical constituents of, 77 712-715  
*Mycobacterium ranac*, isoniazid-dependent strains of, 68 631-633  
*Mycobacterium smegmatis*, intermediary metabolism of glucose by, 73 589-592  
*Mycobacterium tuberculosis*  
   circulating levels of the "plasma factor" responsible for *in vitro* leukocyte cytolysis during sensitization of guinea pigs with, 79 244-245  
   cultivation of Bacille Calmette-Guerin strain of, 78 934-938  
 cultures of  
   collection of sputum for, obtained during local anesthesia prior to bronchography and bronchoscopy, 74 977  
   colorimetric test for measuring catalase activity of, 71 305-307  
   positive, obtained by incubation beyond the

*Notes, Mycobacterium tuberculosis, cont*

- normal 7- or 8-week period, 69 307-308
- preservation of, by freezing, 64 696-697
- detection of
  - in sputum by pepsin digestion and interface concentration with pentane, 75 148-152
  - trisodium phosphate transport-digestion method of processing sputum and gastric specimens for, 70 363-366
- drug susceptibilities of
  - on charcoal agar medium, 71 447-451
  - rapid method for determining, 78 111-116
- gamma-irradiated, and *Brucella suis*, preliminary report on vaccines prepared from, 79 374-377
- growth of, from resected specimens under various atmospheric conditions, 70 910-911
- influence of the size of inoculum on susceptibility testing of, 72 390-392
- isolation of
  - comparative study in, on artificial media and embryonated eggs, 70 912-915
  - comparative study of culture and guinea pig inoculation in, from specimens of human source, 72 687-689
  - evaluation of chick yolk sac method as compared with conventional laboratory procedures for, 77 511-515
- primary
  - development of a rapid microculture technique for, 73 576-580
  - evaluation of blood bank blood agar medium for, from sputum and gastric contents, 71 762-764
  - use of Dubos-type solid medium for, from human discharges, 64 318-321
- isoniazid-resistant
  - atypical histologic aspects of pulmonary tuberculosis as related to attenuation or loss of pathogenicity of, 76 871-876
  - relation of pyrogallol-peroxidative activity to, 75 670-674
- isoniazid-susceptible and -resistant strains, catalase and peroxidase activities, 79 669-671
- PAS-resistant, observations on composition of bacterial population, 77 346-349
- pyrazinamide, lack of significant *in vitro* susceptibility of, on three different solid media, 67 391-395
- selective activity of fluid thioglycolate medium for group differentiation of atypical chromogenic mycobacteria, and saprophytic mycobacteria, 77 356-358
- streptomycin- and isoniazid-resistant strains, further observations on prevalence of, in patients with newly discovered and untreated active pulmonary tuberculosis, 74 293-296
- Vallée strain, immunizing properties of an isoniazid-resistant mutant, as compared with BCG observations in the mouse and guinea pig, 70 527-530
- Mycobacterium tuberculosis* H37Ra, effects of mechanical agitation on the growth of, 79 813-815
- Mycobacterium tuberculosis* H37Rv
  - development of leukocytic susceptibility to tuberculin in guinea pigs experimentally infected with, 76 888-891
  - preliminary observations on development of atypical (chromogenic) variants of, under influence of streptomycin-isoniazid *in vitro*, 78 921-926
  - studies of the catalase activity of, 80 257-258
- neomycin aerosol, results of clinical trial of, in treatment of pulmonary tuberculosis, 78 135-137
- pain, pleuritic, appraisal of theories, 69 634-635
- pancreas, in experimental tuberculosis, guinea pig inoculation via the intraperitoneal route, 78 794-798
- PAS
  - buffered tablets, blood concentration studies with, 72 543-547
  - conjugated, and ascorbic acid and other forms of PAS, studies of
    - comparison of 24-hour blood serum concentrations, 76 880-887
    - patient tolerance, 76 877-879
  - effect of, on silicate restorations (fillings) of teeth, 68 622-624
  - isoniazid, direct antithyroid action of, 71 889-891
  - resin complex, studies in absorption, serum electrolytes, and tolerance, 72 548-551
  - spectrophotometric determination of, and its acetyl derivative in human urine, 64 577-578
- test, urine
  - detection in ambulatory tuberculous patients by, 79 672
  - simple paper strip, 80 585-586
- therapy, prothrombin time during, 2,000 determinations in 400 patients, 67 258-260
- para-isobutoxy benzaldehyde thiosemicarbazone
  - clinical trial in 8 cases of tuberculosis, 68 799-802

*Ver, para el estudio de la enfermedad, con*

failure, as an antituberculosis drug in man, 68 791-793

in the treatment of pulmonary tuberculosis, 68 791-795, 796-798

#### penicillin

as a decontaminant in cultures for tubercle bacilli from undigested sputum, 67 530-531

instability of, in Dubos media, 80 262-263

plasma, influence of tuberculosis on the methylene blue reduction time of serum and heat coagulation value, 70 907-909

pleural effusions, tuberculous, age distribution of, 70 901-902

pleural exudate, bacteriologic study of, following small resections for pulmonary tuberculosis, 73 773-775

pneumothorax, artificial, induction of, 71 596-599

polyoxyethylene ether (Triton WR 1339), failure of, to protect against tuberculin shock in guinea pigs, 79 382-383

polyserositis, tuberculous, 80 259-261

PPD, johnin and tuberculin, sensitization of cattle erythrocytes with, 77 177-180

$\beta$  Propylal- $\gamma$  butylal-imine, new substance with inhibitory effect on *M. tuberculosis* var *hominis* H37Rv, 76 1091-1096

#### pulmonary resection

methods of drainage after, 69 636-637

in the rabbit, 73 123-127

United States Veterans Administration-Armed Forces cooperative studies of tuberculosis results, 1952-1955, 73 960-963

#### pyrazinamide

antituberculosis activity *in vitro* and in the guinea pig, 70 367-369

-cycloserine, in treatment of pulmonary tuberculosis, 76 1097-1099

#### -isoniazid

in patients with previous isoniazid therapy, 75 846-848

therapy, occurrence of hyperuricemia during, 74 289-292

in tuberculosis results in 58 patients with pulmonary lesions one year after the start of therapy, 70 743-747

in low dosage, in combination with isoniazid or PAS in the treatment of pulmonary tuberculosis, 79 102-104

-nicotinamide, activation in acidic environments *in vitro*, 70 748-754

#### pyridoxine

##### -isoniazid

antagonism, delayed appearance of, *in vivo*, 76 1100-1105

concurrent administration of, 74 171-173

radioactive gold (Au<sup>199</sup>)

lymphatic drainage of pericardial space in dogs, as determined by studies with, 76 906-908

lymphatic drainage of pleural space in dogs, as determined by studies with, 75 115-117

reserpine, in treatment of tuberculous mental patients, 71 157-161

riboflavin, as an indicator of isoniazid ingestion in self-medicated patients, 80 415-423

roentgenographic duplication, solarized, 75 139-141

roentgenography, mass, results among immigrants into Israel, 69 837-840

Salizid<sup>®</sup>-isoniazid, antimicrobially active concentration in blood, 74 796-797

#### sarcoidosis

geographic distribution of, 70 899-900

ineffectiveness of isoniazid-isoniazid in therapy of, 67 671-673

secondary factors involved in the etiology of, 71 459-461

serum albumin, factor preventing inhibition of propagation of D-29 mycobacteriophage by Tween<sup>®</sup> in, 80 443-444

serum enzymes in pulmonary tuberculosis, glutamic oxalacetic transaminase and glutamic pyruvic transaminase, 79 251-252

serum lipase, studies, 78 117-120

#### sputum

##### examination

collection and selection, 76 671-674

search for elastic tissue, 76 675-678

search for fungal spores, 76 679-682

tuberculous, preparation for membrane filter filtration, 77 1019-1022

#### streptomycin

-isoniazid-PAS, in treatment of pulmonary tuberculosis, 73 117-122

-susceptible infections, control study of comparative efficacy of isoniazid, streptomycin-isoniazid, and streptomycin-PAS in pulmonary tuberculosis therapy

report on 20-week observations on 390 patients with, 67 108-113

report on 28-week observations on 649 patients with, 67 539-543

report on 40-week observations on 583 patients with, 68 264-269

*Notes, cont*

- streptovaricin
  - alone, in treatment of active pulmonary tuberculosis, 80 426-430
  - alone, and with isoniazid, influence of, in experimental tuberculous infection in animals, and some clinical observations, 75 659-666
- isoniazid
  - controlled clinical trial, 80 757-759
  - in treatment of pulmonary tuberculosis, 80 424-425, 426-430, 431-433
- taurine, in treatment of tuberculosis in guinea pigs, 74 638-640
- thiocarbanidin-isoniazid, clinical evaluation of, in treatment of pulmonary tuberculosis, 80 590-593
- thiocarbanilide SU 1906, pilot study of, in human pulmonary tuberculosis, 74 468-470
- thoracoplasty, constrictive suture (Paulino), 71 892-893
- tranquilizing drugs, effect of, on hospitalized tuberculous patients, 78 127-130, 79 531-532
- triiodothyronine-propyl thiouracil, effect on native resistance to tuberculosis, 73 434-437
- Triton A-20-1,4-dimethyl-7-isopropyl-bicyclo decapentane, experiments on the mechanism of action of, 75 684-687
- Triton WR 1339, and malachite green, use in charcoal media for tubercle bacilli, 71 894-897
- tubercle bacilli
  - cultivation, inspissation of egg media for, 73 139-141
- cultures
  - bluing phenomenon, a source of contamination in, 80 95-99
  - experiments with a new method for, 69 304-306
  - fibrin-clot technique for isolation of, from pleural exudates, 80 438-440
  - filter paper technique for the early detection of microcolonies of, 70 916-919
  - recently isolated, isoniazid susceptibility, catalase activity, and guinea pig virulence of, 73 768-772
  - from resected lung lesions, comparison of bovine albumin and physiologic saline as diluents of tissue homogenates in the recovery of tubercle bacilli by culture and animal inoculation, 70 370-372
  - use of neotetrazolium chloride in, 68 625-628
  - in vivo* method of, the chamber method, 72 393-397
  - cytology, phase contrast studies of changes produced in, during growth, 73 294-295
  - detection of
    - rapid, evaluation of egg embryo as laboratory procedure for, 76 315-319
    - Triton-malachite green-charcoal agar medium for, 75 338-339
  - dilutions
    - instability of potency of, 72 126-128
    - a second report, 74 297-303
  - drug-resistant, rapid detection in sputum by slide cultures, 75 331-333
  - effects of various methods of extraction on the staphylococcal infection-enhancing properties of, 77 1026-1029
  - electron-microscopic and phase contrast studies of effects of PAS, isoniazid, and viomycin on, 73 296-300
  - human, differentiation of, from atypical acid-fast bacilli modification of the niacin test, using Tween®-albumin liquid medium, 79 810-812
  - isolation, relative efficacies of chick embryo and standard ATS media in, from human sputum, 76 703-705
  - isoniazid-resistant
    - catalase activity of, a preliminary report, 69 471-472
    - observations on the pathology of the lesions caused by, in the guinea pig, 74 633-637
    - regression of tuberculous lesions in guinea pigs infected with, 70 531-532
    - study of the virulence of, in guinea pigs and mice a preliminary report, 69 464-468
  - PAS-resistant, genetic considerations of the mechanisms involved in, 79 371-373
  - within pulmonary lesions, effect of degree of healing upon persistence of, 72 386-389
- in the rabbit
  - given cortisone, possible role of humoral factors in enhanced growth of, 77 529-535
  - nature of virulence of human and bovine strains, 67 265-266
- rapid microculture method for isolation of, 75 1007-1008
- from resected pulmonary lesions, influence of quartz on the recoverability of, 71 303-313
- respiratory quotients of, at low oxygen tension, 67 669-670

*Mycobacterium tuberculosis*, cont.

- ring method, for analyzing effect of serum on growth of, *in vitro*, 77 521-528
  - and saprophytic mycobacteria, simple technique for differentiation of, 71 958-960
  - significance of delayed emergence of, 75 506-509
  - in sputum, assay of tuberculous contamination on eating utensils of patients with, 71 162-163
  - suspensions, rapid chemical test for total viability of, 66 95-98
  - tuberculin shock in mice infected with, 68 629-630
  - in tuberculous lesions, use of quartz dust for challenging the viability of, 69 841-842
  - virulent, mixed with BCG, resistance of guinea pigs to infection with small numbers of, 72 539-542
- tuberculin
- effect on oxygen utilization of blood and of splenic tissue from tuberculous and normal guinea pigs, 73 581-585
  - formation, by washed tubercle bacilli, in citrate solution, 67 526-529
- hypersensitivity
- cutaneous, use of tuberculin-treated erythrocytes as antigen in eliciting, 61 322
  - study in 510 patients hospitalized for active pulmonary tuberculosis, 74 474
  - patch test, survey among school age children in Liberia, 67 665-668
  - purified fraction from unheated cultures, in testing BCG-vaccinated subjects, preliminary report, 69 300-303
  - reaction, intracutaneous, effect of topical hydrocortisone acetate ointment at site of, 79 666-668, 80 587-589
- testing
- pilot study for case finding in a general hospital, 79 378-381
  - studies in New York City, 69 1057-1058
- tuberculosis
- antimicrobial therapy, U S Public Health Service cooperative investigation of, report on 32-week observations on combinations of isoniazid, streptomycin, and PAS, 70 521-526
  - bacteriologic media, elimination of precleaning cage laid hens' eggs in preparation of egg fluid, 79 677
  - comparison of roentgenographic and surgical findings in, 71 452-456
  - cost of, estimate for fiscal 1956, 77 172-176
  - drug-susceptibility testing in, 77 350-355

## experimental

- in guinea pigs, effects of phagocytic stimulation on, 73 442-443
  - in mice, control of, by intermittent administration of streptomycin, viomycin, isoniazid, and streptomycyclidene isonicotinyl hydrazine, 68 292-291
  - short-term therapy, 77 867-868
  - miliary and meningeal, in childhood, in New York City, 77 359-363
- mortality
- current analysis of, in New York City, 77 516-518
  - in Puerto Rico since 1950, 70 1099-1101
  - rates, among World War II veterans (a screened population) for the years 1953 and 1954, further report on, 73 966
- pulmonary
- problems in surgical management of, 76 902-905
  - rapid mouse test for diagnosis of enhancement of experimental tuberculosis in mice by hog gastric mucin, 77 1005-1011
  - preliminary studies with patients' specimens, 77 1012-1016
  - results of an international survey of, 73 128-133
  - surgical pathology of isoniazid-treated, 68 144-149
  - susceptibility, of normal and immunized mice, relationship of sex to, 80 750-752
- tuberculous cavities, giant cells lining healing, 78 140-144
- tuberculous infection, during academic studies, 76 308-314
- tuberculous patient, uncooperative, compulsory isolation of, experience in the state of Georgia, 77 506-510
- tuberculostatic agent, present in animal tissues, 63 119
- tuberculostatic factor, in normal human urine, 73 967
- ultrafiltration, improved apparatus, 63 718-720
- vaccination, antituberculosis, in guinea pig, with nonliving vaccines, 77 719-724
- vaccine, irradiated, trials with, 75 987-991
- viomycin, in the re-treatment of pulmonary tuberculosis, 72 843-845
- X-ray viewer, new multipurpose, magnifying, 68 788-790
- Zephiran®, use of, in the isolation of *M. tuberculosis*, 74 284-288
- Novobiocin, 76 272-278
- in murine leprosy, 79 673-676



W-95.8625; when TD = transverse diameter (in mm.); A = age (in years); H = height (in inches) and W = weight (in pounds). This formula was suggested after a study of 80 subjects had been made in which there was no evidence of cardiac pathology. A later article by Eyster (13), in which another 100 patients were added to the original, showed that 3 per cent exceeded the predicted transverse diameter by more than 10 per cent, which means that it is 19 per cent more efficient than assuming an average for all cases.

In their original article the authors pointed out that, of the variables, weight exerted the greatest effect on the transverse diameter. Age was next in importance and height affects the transverse diameter least.

TABLE 1

*A tabulated summary showing age distribution and a comparison of the measured transverse diameter (MTD) and the predicted transverse diameter (PTD) of the different age groups*

AGE	NUMBER OF CASES	PER CENT	MTD > PTD		MTD < PTD		MTD = PTD	
			Number	Per cent	Number	Per cent	Number	Per cent
<i>years</i>								
18-20	6	1.5	4	66.6	2	33.3		
20-30	176	44	85	48.4	76	43.1	15	8.5
30-40	142	35.3	78	24.6	24	37.8	10	7.7
40-50	50	12.5	26	52	21	42	3	6
50-60	25	6.25	10	40	11	44	4	16
60-67	1	.25						
All ages . . .	400		203	50.5	165	41.5	32	8

## DATA

The present report is the result of a study made of the teleoroentgenograms of 400 patients who had pulmonary tuberculosis. Of this number 54, or 13.5 per cent, are dead. Of the remaining 346, some are still in the hospital under treatment, some were discharged as apparently arrested, while others left the hospital against medical advice. Therefore it is quite possible that more than 54 are now dead but we have no record to show this to be true.

All of the patients were male beneficiaries of the United States Marine Hospital, and had been sent to Fort Stanton for the treatment of pulmonary tuberculosis. The age range was from 18 to 67 years, and age distribution was as follows: from eighteen to twenty, 6 (1.5 per cent); twenty to thirty, 176 (44 per cent); thirty to forty, 142 (35.5 per cent);

forty to fifty, 50 (12.5 per cent); fifty to sixty, 25 (6.25 per cent); sixty to sixty-seven, 1 (.25 per cent).

Essentially all types of pulmonary tuberculosis were represented in this group.

The transverse diameter was measured from the original X-ray film in practically all instances. The predicted diameter was computed on

TABLE 2

*A summary showing the age distribution of the deaths and a comparison of the measured transverse diameter (MTD) and the predicted transverse diameter (PTD) of the different age groups*

AGE	NUMBER OF DEATHS	PER CENT	MTD > PTD		MTD < PTD		MTD = PTD	
			Number	Per cent	Number	Per cent	Number	Per cent
<i>years</i>								
20-30	30	55.5	14	46.6	12	40	4	13.3
30-40	13	24	9	69.2	3	23	1	7.7
40-50	8	14	3	37.5	5	62.5		
50-60	3	5	1	33.3	1	33.3	1	33.3
All ages....	54		25	46.29	23	42.59	6	11.12

TABLE 3

*A group summary of the average age, height, admission weight, normal weight, measured transverse diameter, predicted transverse diameter and predicted transverse diameter on the basis of the normal weight of the various age groups*

AGE	AVERAGE AGE	AVERAGE HEIGHT	AVERAGE ADMISSION WEIGHT	AVERAGE WEIGHT NORMAL	AVERAGE MTD	AVERAGE PTD	PTD ON BASIS OF NORMAL WEIGHT
<i>years</i>	<i>years</i>	<i>inches</i>	<i>pounds</i>		<i>mm.</i>	<i>mm.</i>	
18-20	18.66	69.3	139	146	115	112.4	117.9
20-30	24.4	68.6	141.8	150	116.3	116.7	120.9
30-40	34	68.8	144	155	121.5	118.99	125
40-50	44.3	68.8	144	154	121.6	120	123.4
50-60	55.4	70	143	156	117.9	118.6	124
60-67	67	66	141	160	120	122	122

the basis of admission age, admission weight, and admission height. The normal weight of the patient was also recorded on his admission to the hospital. Therefore the measured cardiac diameter at the time of entrance to the hospital was compared with the predicted diameter using both the admission weight and the patient's normal weight.

After the computation had been made, the cases were grouped according to age, and a survey was made to determine in how many instances

the heart was smaller than the predicted normal, larger than the predicted normal or the same as the predicted normal. The results are shown in table 1.

The deaths were separated from the entire group and a similar tabulation was made (table 2).

A grand average for age, height, admission weight, normal weight, and predicted diameter of the different age groups is recorded in table 3.

#### REMARKS

In this study, as is often the case in clinical investigation, our aim was to establish proof to a belief, namely that the heart of the individual having pulmonary tuberculosis is smaller than the predicted normal on the basis of weight, height and age. We found, however, that this was not true of this group of four hundred. We do not wish to draw conclusions from our study. We are merely summarizing our findings. Whether or not the altitude of the hospital, which is 6000 feet above sea level, has any influence on the size of the cardiac shadow is a matter for speculation.

#### SUMMARY

1. A study was made of the teleoroentgenograms of 400 patients having pulmonary tuberculosis.
2. Their ages range from 18 to 67 years.
3. The study included all clinical types of pulmonary tuberculosis.
4. A comparison was made between the measured transverse diameter of the heart and the predicted transverse diameter.
5. Of the 400 cases, 203 (50.5 per cent) had a measured transverse diameter greater than the predicted diameter, 165 (41.5 per cent) had a measured transverse diameter of less than the predicted diameter and 32 (8 per cent) had a measured transverse diameter equal to the predicted diameter.
6. As is shown in table 2, in a study of the X-ray films of the 54 cases that died, there was very little difference noticed as compared with the general average.

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*Para aminosalicylic acid, -streptomycin, cont*

- effect on tubercle bacilli *in vitro* and *in vivo*, 59 554-561
- stilbamidine in pulmonary tuberculosis and systemic blastomycosis, (case reports) 68 615-621
- in pulmonary tuberculosis, (Notes) 72 242-244
- sustained-action tablets, blood concentrations with, (Notes) 77 184-188
- therapy, prothrombin time determinations during, (Notes) 67 258-260
- toxic reaction to, accompanied by leukopenia and lymphocytosis, (case reports) 69 824-828
- in tuberculosis
  - experimental
    - in guinea pigs
      - combined with dihydrostreptomycin alone or with Tibione, 63 339-345
      - single and double daily doses of, 78 753-759
    - in mice, inability to delay emergence of streptomycin-resistant tubercle bacilli in, 62 156-159
  - extrapulmonary, 61 613-620
  - intestinal, 61 621-642
  - pulmonary, 61 226-246, 597-612, 613-620, (Notes) 73 117-122
    - dosage forms, 62 610-617
    - febrile reactions, 61 643-647
    - hypopotassemia and hyponatremia during treatment, 66 357-363
    - intermittent regimens, combined with streptomycin in treatment of, 63 295-311
    - with pyrazinamide or isoniazid, (Notes) 79 102-104
  - urine test for detection in ambulatory tuberculous patients, (Notes) 79 672
- Para-(di-*n*-propylsulfamyl)-benzoic acid, influence on PAS plasma concentrations, 61 862-867, 64 448-452, 453-460
- Para ethylsulfonyl benzaldehyde thiosemicarbazone *See* Thiosemicarbazones
- Para-formylacetanilide thiosemicarbazone *See* Thiosemicarbazones
- Para-isobutyrylbenzaldehyde *See* Thiosemicarbazones
- Paralysis
  - of phrenic nerve *See* Phrenic nerve
  - recurrent, of laryngeal nerve, as complication of pulmonary tuberculosis, 65 93-99
  - of vocal cords, 73 52-60
- Paratubercle bacilli, skin reaction to products of, 79 731-737
- Parkinson's syndrome, dyspnea in, 78 682-691
- Paromomycin, in murine leprosy, (Notes) 79 673-676

PAS *See* Para-aminosalicylic acid

## Pathogenicity

- loss or attenuation, in pulmonary tuberculosis, during prolonged chemotherapy, (Notes) 76 871-876
- of streptomycin-dependent tubercle bacilli, 63 96-99

## Pathogenesis

- of emphysema, 62 45-57
- of extrapulmonary tuberculosis, 62 (Supplement, July 48-67)

## Pathology of tuberculous meningitis, effect of streptomycin on, 61 171-184

## Patient(s)

- and physician, 62 (Supplement, July 68-75)
- tuberculous
  - behavior rating, 70 483-489
  - education for, 70 490-497
  - evaluation of attitude, 67 722-731
  - leaving hospital against advice, personality characteristics, 67 432-439

## Paulino procedure, (Notes) 71 892-893

## Peliosis hepatis, 67 385-390

## Pembine type case conference, consecutive, manual for, 79 258-263

## Penal institutions, pulmonary tuberculosis in, 61 51-56

## Penicillin

- as decontaminant in cultures for tubercle bacilli from undigested sputum, (Notes) 67 530-534
- instability, in Dubos media, (Notes) 80 262-263
- susceptibility
  - of human acid-fast bacilli, nontuberculous, (Notes) 75 675-677
  - and virulence, in *M. tuberculosis*, 80 849-854
- in wound infection after thoracoplasty, 61 346-352

Pentane, concentration of *M. tuberculosis* in sputum, (Notes) 75 148-152Pepsin digestion, of *M. tuberculosis* in sputum, (Notes) 75 148-152Peptic ulcer *See* UlcersPeptone, inhibition of sporulation of *C. immittis* by, (Notes) 74 147-148

## Periarteritis

- nodosa, lung cavitation in, (case reports) 74 621-632
- with sarcoidosis, (case reports) 60 236-245

## Pericarditis

- chronic, biopsy in, 75 469-475
- and lymphatic drainage, (Notes) 76 905-908
- in mediastinal tuberculosis, (case reports) 79 238-243

## in tuberculosis sanatorium, 76 636-642

## tuberculous, 59 650-655

## streptomycin in, 59 656-663

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*Pleurisy, tuberculous cont*

- and osteogenesis imperfecta, (case reports) 67 514-516
- primary, with effusion, antimicrobial therapy in, 74 897-902

**Plombage**

Ivalon sponge, (Notes) 78 478-484

**Lucite**

ball, extraperiosteal, 68 902-911

fatal asphyxia from, (case reports) 61 422-425

**Pneumatosis cystoides intestinalis**, (case reports) 72 373-380

**Pneumocele(s)**

abdominal, following artificial pneumoperitoneum, (case reports) 60 520-523

diaphragmatic, in therapeutic pneumoperitoneum, 69 745-758

scrotal, during pneumoperitoneum, (case reports) 74 622-623

**Pneumococcosis and tuberculosis**, 3, 3', 5-triiodo-L-thyronine in survival time of mice, 79 339-343

**Pneumoconioses**

anthracite coal miners (100)

with pulmonary complaints, respiratory gas exchange studies in, 61 201-225

with respiratory complaints, pulmonary emphysema and ventilation measurements in, 59 270-288

**anthracosilicosis**

cavitation in, 71 544-555

tuberculosis in, 65 24-47

**beryllium****case registry**

establishment of, (correspondence) 68 941-942

at Massachusetts General Hospital, (correspondence) 72 129-132

compounds, granulomatosis following exposure to, 60 755-772, 62 29-44, 65 142-158, 74 533-540

poisoning, and sarcoidosis, 74 885-896

workers, dyspnea in, 59 364-390

**Caplan's syndrome**, (case reports) 78 274-281

from diatomaceous earth, coalescent lesion of, 77 644-661

dusts, industrial, individual susceptibility to, 62 (Supplement, July 13-21)

**granulomatosis****pulmonary**

from beryllium, 74 533-540

in beryllium workers, dyspnea in, 59 364-390

chronic, in beryllium workers, 62 29-44

diffuse, after exposure to beryllium, 60 755-772, 65 142-158

**quartz dust**

for challenging viability of tubercle bacilli

in tuberculous lesions, (Notes) 69 841-842

in demonstration of viable tubercle bacilli in resected lesion after chemotherapy, (Notes) 71 144-145

effect on recoverability of tubercle bacilli from resected pulmonary lesions, (Notes) 71 308-313

in experimental silicosis in guinea pigs, 69 766-789

inhalation of, influence on tuberculous infection by BCG, H37Ra, and *M marinum*, 69 763-789

**silicosis**

and avian tuberculosis, (case reports) 80 78-84

BCG vaccination in, 62 455-474, 69 763-789

and bronchogenic carcinoma, (case reports) 76 1088-1093

of gold miners, lung function in, 77 400-412

of other workers, (case reports) 77 839-847

pneumolitis in, (case reports) 79 512-517

**silicotuberculosis**

resection in, (case reports) 71 137-139

therapy, medical and medical surgical, in, 78 524-535

tuberculosilicosis, surgical therapy in, 77 62-72

tuberculosis complicating, chemotherapy in, (correspondence) 79 818

welders, respiratory disorders in, (case reports) 71 877-884

**Pneumoencephalography** in tuberculous meningitis, 74 835-855

**Pneumolitis** in silicosis, (case reports) 79 512-517

**Pneumonectomy**

for pulmonary hemorrhage in tuberculosis, (case reports) 61 426-430

in pulmonary tuberculosis, 77 73-82, 260-270, 78 822-831

pregnancy after, 78 563-579

spontaneous pneumothorax after, (case reports) 62 116-117

and streptomycin, in streptomycin-refractory pulmonary tuberculosis, (case reports) 66 605-614

**Pneumonia**

acute, and bronchiectasis, 76 761-769

and bronchogenic carcinoma, in adults, 76 47-63

Friedlander's, 61 465-473

hypoid, (case reports) 64 572-576

tuberculin-induced, in lungs of sensitized rabbits, adrenocorticotrophic hormone in, 64 508-515

**tuberculous**

due to organisms resistant to streptomycin and isoniazid, (case reports) 70 881-891

massive, management of, 64 41-49

- Tuberculosis, tuberculous*  
 in Negroes, 68 382-92  
 streptomycin therapy in, 69 313-353
- Pneumonitis, Löffler's during antituberculosis chemotherapy, (case reports) 71 115-153
- Pneumolysis, intrapleural, closed, 59 210-255
- Pneumoperitoneum  
 air embolism in, 69 396-405, (case reports) 72 537-538  
 appendicitis during 61 353-354  
 artificial  
 abdominal pneumocele after, (case reports) 69 520-523  
 complications of, 61 645-658  
 effect of ballistocardiograms of patients with chronic disease, 66 52-57  
 compared with pregnancy in young women with functionally normal lungs and serial observations during pregnancy and postpartum pneumoperitoneum, 67 765-778  
 complicated by pneumothorax, (case reports) 63 710-713  
 left-sided, (case reports) 72 663-666  
 and peritoneal effusion, (case reports) 66 90-94  
 ruptured diaphragm resulting in spontaneous, (case reports) 63 587-590  
 complicated by serotal pneumocele, (case reports) 71 622-623  
 electrocardiogram in, 61 315-315  
 diaphragmatic rupture and vital tension pneumothorax, (case reports) 60 791-800  
 gastrointestinal changes in, 66 750-757  
 hepatitis in, (case reports) 69 297-299  
 induction, complicated by mediastinal emphysema, (case reports) 63 591-596  
 inflation of esophageal hernial sac during, (case reports) 75 823-827  
 with inguinal hernia, (case reports) 60 521-526  
 intraperitoneal hemorrhage in  
 caused by splenic rupture after, (case reports) 77 291-294  
 occurring as complication of, 63 116-118  
 mediastinal emphysema after, (case reports) 63 775-781  
 and millwheel murmur presumably caused by air embolism, (case reports) 70 1092-1095  
 in nonsurgical treatment of esophageal hiatal hernia, (case reports) 78 623-631  
 pelvic complications of, (case reports) 62 109-111  
 with phrenic paralysis for pulmonary tuberculosis, 61 323-331  
 physiologic effects on respiratory apparatus, 60 706-711  
 with pregnancy, (case reports) 62 219-222, 66 86-89  
 in pulmonary tuberculosis  
 effect on liver function, 65 589-595  
 respiratory effect of, 70 472-688  
 spirometric studies in, 65 465-476  
 spontaneous pneumothorax after, (case reports) 71 295-298  
 with streptomycin-PAS, in pulmonary tuberculosis, 69 963-967  
 sulfur hexafluoride in, 76 1065-1070  
 tenacious of, 63 62-69  
 therapeutic  
 complicated by mediastinal emphysema, (Notes) 76 897-898  
 diaphragmatic pneumocele in, 69 745-758  
 with spontaneous right-sided pneumothorax, 63 67-75  
 with torsion of the spleen, (case reports) 62 439-440, 70 166-170, correspondence) 70 923  
 transdiaphragmatic extrusion in, (case reports) 69 1015-1030
- Pneumotherapy and chemotherapy, possible antagonism (correspondence) 70 533-534, 71 690-692, 71 766
- Pneumothorax  
 artificial, (correspondence) 72 252, 694  
 angiocardiology in, 62 353-359  
 induction, (correspondence) 69 511-515, (Notes) 71 596-599  
 in lower lobe tuberculosis, 79 50-52  
 in middle-aged and elderly patients, 69 268-279  
 statistical analysis of 557 cases initiated in 1930-1939 and followed in 1949  
 I Influence of clinical findings before induction and late results, 64 1-20  
 II Fate of the contralateral lung, 64 21-26  
 III Influence of features of management after induction on early and late results, 64 27-40  
 IV Incidence, mortality, and factors associated with complicating tuberculous emphysema, 64 127-140  
 V Incidence, degree, and causative factors of pulmonary contraction or "unexpandable lung," 64 141-150  
 VI Results in various selected series of cases, 64 151-158  
 complication of pneumoperitoneum, (case reports) 63 710-713  
 extrapleural, 67 3-21  
 complicated by extrapleural hematoma, streptokinase-streptodornase in, 63 547-555  
 fluid, functional prophylaxis in, 66 131-150  
 induction, (correspondence) 70 373-374, 755, 72 268-273

*Pneumothorax induction cont*

- lung trauma at, 60 557-563
- traumatic, (correspondence) 70 536-537
- left sided, complicating pneumoperitoneum, (case reports) 72 663-666
- by lung puncture or "orthodox" technique, (editorials) 69 121-124
- machines and needles, historic collection, (correspondence) 80 278
- recurrent, 60 683-698
- spontaneous, 72 257-267
  - bilateral, and spontaneous mediastinal emphysema, (case reports) 61 883-886
  - in histoplasmosis, complicated by pregnancy, (case reports) 75 111-121
  - nontuberculous, 60 683-698
  - after pneumonectomy, (case reports) 62 116-117
  - after pneumoperitoneum, (case reports) 71 295-298
  - in pulmonary tuberculosis, 74 351-357
  - resection, 72 801-809
  - result of ruptured diaphragm complicating pneumoperitoneum, (case reports) 63 587-590
  - right-sided, complicating pneumoperitoneum, 63 67-75, (case reports) 66 90-94
- and streptomycin, in pulmonary tuberculosis, 59 539-553
- tension, following diaphragmatic rupture during pneumoperitoneum, (case reports) 60 794-800
- therapeutic,
  - with massive hemothorax, (case reports) 60 654-659
  - in middle-aged and elderly patients, 63 325-331
  - present status, 62 (Supplement, July 90-97)
- tuberculous, spontaneous, 59 619-623
- Polycythemia
  - idiopathic hypoventilation, and cor pulmonale, (case reports) 80 575-581
  - with tuberculosis of spleen, (case reports) 60 660-669
- Polyoxyethylene ether *See also* Triton WR 1339
  - action against tubercle bacilli, 69 690-704
  - failure to protect against tuberculin shock in guinea pigs, (Notes) 79 382-383
- Polysaccharide(s)
  - chemical and biological properties, 59 86-101
  - isolation by alcohol fractionation from tuberculin of, 59 86-101
  - serum, during sensitization and development of tuberculosis, 62 67-76
- skin tests
  - Blastomyces dermatitidis* and *H. capsulatum*, in humans, (Notes) 80 264-266
  - reactions, 77 983-989
  - in tuberculosis, interference with antibodies, 73 547-562
- Polyserositis, tuberculous, (Notes) 80 259-261
- Polyvinyl-formal sponge prosthesis in pulmonary diseases, 74 581-589
- Potassium para-aminosalicylate, clinical use, 71 220-227
- Potassium iodide
  - PAS, in chronic fibroid tuberculosis, 64 77-80
  - streptomycin in experimental tuberculosis in guinea pigs, 64 102-112, 66 680-698
- Pott's disease, 62 (Supplement, July 48-67)
- PPD *See* Tuberculin
- Precipitin
  - agar diffusion techniques, 73 637-649
  - test for carbohydrate antibodies in tuberculosis in humans, (correspondence) 59 710-712
- Prednisone *See* Hormones
- Pregnancy
  - complicating artificial pneumoperitoneum, 62 219-222
  - complicating chronic pulmonary histoplasmosis with spontaneous pneumothorax, (case reports) 75 111-121
  - full-term, after thoracic surgery for tuberculosis, 78 697-711
  - and mihiary tuberculosis, 62 209-212
  - in tuberculous salpingitis causing acute hematogenous tuberculosis, (case reports) 68 253-262
  - pneumoperitoneum during, (case reports) 66 86-89
  - pulmonary function in
    - comparison of pneumoperitoneum and pregnancy in young women with functionally normal lungs, and serial observations during pregnancy and postpartum pneumoperitoneum, 67 755-778
    - serial observations
      - in normal women, 67 568-597
      - in patients with pulmonary insufficiency, 67 779-797
    - and sarcoidosis, (case reports) 63 603-607
    - tuberculous meningitis during, (case reports) 76 1079-1087
    - in tuberculous mother, 65 1-23
- Pressure, pulmonary arterial, and tuberculosis frequency, 78 536-546
- Pressure-flow-volume interrelationships in man, 80 (Supplement, July 138-140)
- Prevention in tuberculosis, (editorials) 74 117-120
- Primary tuberculous focus, local reactivation in lung, 78 547-562
- Prisoners, mass screening program of, in Los Angeles County jail, 74 590-596



- Probencid  
   effect on blood PAS concentrations, 66 228-232  
   influence on PAS plasma concentrations, 61 862-867  
 Procrustes? See Thiazolsulfone  
 Prophylactic effects of isoniazid in primary tuberculosis, 76 412-463  
 Prophylaxis  
   isoniazid  
     in nontuberculous disease, (correspondence) 75 485-487  
     in experimental tuberculosis, 77 999-1004  
   of tuberculosis in children, 71 (Supplement, August 75-83)  
 Propylthiouracil, and triiodothyronine, in experimental tuberculosis, (Notes) 73 431-437  
 Protein(s)  
   antituberculous, in bovine spleen, 75 493-499  
   in caseous necrosis, 77 109-119  
   fraction  
     of *M. tuberculosis*, isolation and chemistry of, and its ability to sensitize cells, 66 314-331  
   serum, electrophoretic and chemical, in pulmonary tuberculosis, 67 299-321  
   isolation by alcohol fractionation from tuberculin, 59 511-518, 519-538  
   oral hydrolysate, in pulmonary tuberculosis, 59 511-518, 519-538  
   from paratubercle bacilli, reaction of, and OT, 79 731-737  
   in pleural effusions, 76 217-235  
   purified, derivative, comparison with a purified tuberculin, 66 315-350  
   serum  
     changes, in experimental tuberculosis, 77 120-133  
     electrophoretic  
       and isoniazid therapy, 70 331-343  
       and Middlebrook Dubos titer in BCG vaccinated tuberculous children, (Notes) 79 522-524  
       in tuberculosis, 68 372-381  
       in tuberculous guinea pigs, 70 311-318  
   therapy, in pulmonary tuberculosis, 59 511-518, 519-538  
   tuberculin and johnin, fractionation of, 68 425-438, 439-443, 444-450  
 Proteinosis, alveolar pulmonary, (case reports) 78 906-915, 80 219-251  
 Prothrombin time determinations during PAS therapy, (Notes) 67 258-260  
 Pseudocavities, roentgenographic, 71 529-543  
*Pseudomonas aeruginosa*, self inoculation with, by a diabetic woman, (case reports) 69 818-823  
 Prtittacosis, antibodies in, tetracycline influence on, 71 569-571  
 Psychologic scale for irregular discharge prediction, 71 338-350  
 Psycholo, in tuberculosis, 71 201-219  
 Psychosis  
   in tuberculous patients, 59 289-310, 72 107-116  
     collapse therapy in, 67 232-246  
     toxic, from isoniazid, (case reports) 79 799-804  
 Psycho-social factors in pulmonary tuberculosis, 75 768-789  
 Psychotic, tuberculosis in, (editorials), 68 782-785  
 Puerto Rico  
   tuberculosis in, 67 132-153  
     childhood, 76 388-397  
     mortality, since 1950, (Notes) 70 1099-1101  
 Pulmonary With the exception of Pulmonary function, below, see listings under Lungs and specific conditions  
 Pulmonary function  
   air velocity index, 62 17-28  
   airways obstruction, chronic, pulmonary diffusion in, 71 219-259  
   alveolar arterial oxygen tension gradient in pulmonary disease, 69 71-77  
   alveolar capillary block from leukemic infiltration of lung, (case reports) 80 895-901  
   alveolar respiratory surface, effective, and other lung properties in normal persons, 70 296-303  
   arterial oxygen lack measured by oxygen tension, 79 315-322  
   Bellows apparatus in studies, 80 721-731  
   bilateral residual volume determination  
     in healthy subjects, 78 368-375  
     in tuberculous subjects, 78 376-390  
   blood flow through nonventilated portions of lung, 68 177-187  
   in bronchitis, physiologic defects in, 78 191-202  
   bronchospirrometry  
     after pulmonary decortication, 66 509-521  
     before and after segmental resection and lobectomy for, 75 710-723  
     in thoracic surgery, 75 730-741  
     before and after thoracoplasty, 75 724-729  
     values, significance of, 75 699-709  
     vital capacity in, (Notes) 76 320-321  
   after bullae excision, 77 387-399  
   carbon dioxide narcosis treated by resuscitator, 71 309-316  
   carbon monoxide diffusing capacity during exercise, 74 317-342  
   cardiopulmonary function  
     in Boeck's sarcoid, cortisone in, 67 154-172

*Pulmonary function, cardiopulmonary function cont*

- in bronchiectasis, pre- and postoperative, 69 869-914
- in emphysema *See* emphysema, below
- in hematogenous pulmonary tuberculosis in patients receiving streptomycin, 64 583-601
- in pulmonary fibrosis, 80 700-704
- circulation
  - in emphysema *See* emphysema, below
  - pulmonary capillary, 71 822-829
- coal miners, respiratory gas exchange in, 61 201-225
- corticotropin-cortisone effects on, 64 279-294
- after decortication, 63 231-251
  - bronchspirometric study, 66 509-521
- diffusing capacity
  - during exercise, 80 806-824
  - without airway obstruction, 78 173-179
- dyspnea in beryllium workers, 59 364-390
- in emphysema
  - air flow physics in, 80 (Supplement, July 123-125)
  - bullous, bilateral, (case reports) 71 867-876
  - chronic
    - energy cost and control of breathing, 80 (Supplement, July 131)
    - obstructive, cardiopulmonary function in, 80 689-699
    - pressure-volume and pressure-flow relationships, 74 210-219
    - respirators in, 80 510-521
    - routine tests in correlation of compliance and mechanical resistance, 74 220-228
  - circulation dynamics in, during exercise, 80 (Supplement, July 128)
  - in coal miners, ventilatory measurements in, 59 270-288
  - diagnosis of, oximeter test in, 80 705-715
  - diffusing capacity in, 71 249-259
  - intermittent positive pressure breathing in, 76 33-46
  - mechanics of ventilation in, 80 (Supplement, July 118-122)
- functional residual capacity measured with two closed-circuit helium-dilution methods, 74 729-738
- gas mixing in tuberculous lung, 74 343-350
- idiopathic hypoventilation, polycythemia, and cor pulmonale, (case reports) 80 575-581
- impaired function, basal respiratory minute volume as index of, 65 505-510
- intermittent positive pressure breathing
  - in bronchopulmonary disease, 71 693-703
  - in emphysema, severe, pulmonary, 76 33-46
  - in tuberculosis, pulmonary, 72 479-486
- intrapulmonary gas mixing after lung surgery for tuberculosis, 78 1-7
- maximal breathing capacity, predicted, in obese subjects, (Notes) 80 902-903
- mechanics of breathing
  - effects of smoking on, 77 1-16
  - gas exchange, and pulmonary circulation, influence of ventilatory mechanics, 80 53-58
  - physical properties of lung, 80 38-45
  - respiratory work, 80 46-52
- in mitral stenosis, 79 265-272
- oxygen
  - breathing, in respiratory acidosis, 77 737-748
  - diffusing capacity during exercise, 80 806-824
- Parkinson's syndrome, dyspnea as symptom, 78 682-691
- after phrenic crush, 71 676-692
- pneumoperitoneum effects
  - physiologic, 60 706-714
  - in pulmonary tuberculosis, 70 672-688
- in pregnancy, 67 568-597, 755-778, 779-797
- pressure-flow-volume interrelationships in man, 80 (Supplement, July 138-140)
- in pulmonary tuberculosis, 79 474-483
- reflex responses to inflation or deflation of lungs and role in respiratory regulation 73 519-528
- in resection
  - bilateral, 79 468-473
  - partial, functional results after, 76 983-987
  - pulmonary, before and after, 72 453-464
  - segmental, for bronchiectasis, 77 209-220
- residual air measurements by helium and oxygen, 76 601-615
- respiratory disorders in welders, (case reports) 71 877-884
- respiratory infection, importance of, 64 461-467
- in silicosis in gold miners of Witwatersrand, 77 400-412
- spirometers, aneroid and water compared, 61 582-585
- spirometry
  - in maximal breathing capacity, compared with Douglas Bag measurement, (Notes) 79 253-255
  - in pneumoperitoneum, 65 465-476
- tests, 79 457-467
  - direct-writing ear oximeter in, 74 511-532
  - in evaluating patients for thoracoplasty, 63 76-80
  - index of expiratory force, 78 692-696
  - maximal midexpiratory flow, 72 783-800
    - for detecting ventilatory obstruction, 78 180-190

# *Index for subjects*

- Report of the AIS Subcommittee 62 151-154
  - sample, for sanatorium or clinic, 60 149-167
  - simple breath oxygen, terminal rise in, 75 745-755
  - in tuberculosis, 71 330-348
    - and other chronic pulmonary diseases 70 142-151
  - ventilation
    - defective, analysis by timed capacity measurements, 61 250-275
    - disturbances determined by helium dilution method, 70 170-179
    - efficiency, nitrogen clearance in, 72 165-178
    - measurement, convenient method based on Venturi principle, 75 303-318
  - Purified protein derivative *See* Tuberculin, PPD
  - Purpura, thrombocytopenic, and bronchogenic carcinoma, (case reports) 67 509-513
  - Pyrazinamide
    - activation in acidic environments *in vitro*, (Notes) 70 748-751
    - alone and in combination in experimental tuberculosis, 76 643-659
    - antituberculosis activity *in vitro* and in guinea pigs, (Notes) 70 367-369
    - AIS statement on, 75 1012-1015
    - cycloserine, in pulmonary tuberculosis, (Notes) 78 927-931
    - hepatotoxicity, 80 371-387
    - induced liver damage, by serum enzyme determinations, 80 855-865
    - inducing hepatitis, (case reports) 77 858-862
    - isoniazid
      - causing hyperuricemia, (Notes) 74 289-292
      - compared with isoniazid-PAS, 73 704-715
      - in experimental tuberculosis, 69 319-333
      - in low dosage, 74 400-409
      - in patients with previous isoniazid therapy, (Notes) 75 816-818
      - in pulmonary tuberculosis, 69 319-350
      - with isoniazid, (Notes) 70 743-747
    - in tuberculosis, (Notes) 72 851-855
    - lack of significant *in vitro* susceptibility of *M. tuberculosis* to, on solid media, 67 391-395
    - measurement, in blood and kidneys, 75 105-110
    - nicotinamide, intracellular activation of, 74 718-728
    - paired with other drug combinations, 80 627-640
    - resistant tubercle bacilli, 74 572-580
    - susceptibility
      - of isoniazid resistant tubercle bacilli, (Notes) 72 840-842
      - in vitro*, of tubercle bacilli to, (Notes) 65 635-636
    - toxicity, 70 423-429
    - in tuberculosis
      - experimental
        - in guinea pigs, 65 519-522
        - in mice, 65 511-518
      - pulmonary, 65 523-546, (case reports) 69 143-159, (Notes) 76 1097-1099
      - alone and in combination with streptomycin, PAS, or isoniazid, 70 113-122
      - with isoniazid or PAS, (Notes) 79 102-104
      - viomycin, in surgical therapy of tuberculosis, 77 83-92
  - Pyridine derivative in experimental tuberculosis, (correspondence) 60 269-271
  - Pyridine nucleotides in experimental tuberculosis, before and during isoniazid therapy, 70 453-464
  - Pyridoxal, neutralization of isoniazid, 76 568-578
  - Pyridoxine
    - isoniazid
      - concurrently administered, (Notes) 74 471-473
      - delay of antagonism *in vivo*, (Notes) 76 1100-1105
      - effect on
        - antituberculosis activity *in vivo*, (Notes) 71 898-899
        - metabolism, 75 594-600
      - massive dose, in pulmonary tuberculosis, 78 474-477
      - relationship in children, 75 594-600
  - Pyrogallol peroxidative activity, relationship to isoniazid resistance in *M. tuberculosis*, (Notes) 75 670-674
- ## Q
- Quaternary ammonium compounds, and pancreaticatin, in sputum cultures, 72 98-106
  - Quartz *See* Pneumoconiosis
- ## R
- Rabbits *See* Tuberculosis, experimental
  - Radioactive iodine ( $I^{131}$ ) in chronic pulmonary insufficiency, 80 181-187
  - Radiation
    - effects and protection from, in chest roentgenographic surveys, (ATS statement) 80 115-117
    - hazard
      - in photofluorography, method to reduce, 77 923-930
      - in roentgenography, 77 203-209, 375-386
    - therapy
      - in middle lobe syndrome in children, (case reports) 76 291-297

From table 6, we see that a higher percentage of those children who were exposed to open tuberculosis within three months prior to vaccination developed a positive Mantoux reaction than children not exposed. There are several possible explanations for this unexpected finding. It may be a purely accidental finding; or a number of the children who were exposed to open tuberculosis, and gave a negative tuberculin reaction at the time of vaccination, may have already been naturally infected, and been in the preallergic incubation period of tuberculosis; or many of the children exposed to open tuberculosis before vaccination continued to be exposed after vaccination as well. The greater incidence of allergy in the exposed group may very well be due to the subsequent exposure rather than that which preceded the vaccination.

We would naturally expect exposure following vaccination to affect the incidence of the development of allergy, since some of the children exposed to open tuberculosis may become naturally infected. Aronson and Dannenberg (7), in a study of 70 orally vaccinated infants, found no definite relationship between the incidence of allergy and the type of exposure following vaccination. They report positive tuberculin reactions in 82 per cent of the cases exposed to open tuberculosis, in 93 per cent exposed to closed tuberculosis, and in 75 per cent who were not exposed. Turpin (8), however, found 10 to 20 per cent more positive reactors in a group of orally and parenterally vaccinated children who lived in a tuberculous environment as compared to a vaccinated group in a nontuberculous environment.

The positive tuberculin test produced by BCG vaccination is not a permanent phenomenon. In a considerable percentage of the cases the tuberculin allergy becomes less intensive between six and twelve months after vaccination and gradually becomes negative after twelve months.

The relative number of disappearing positive Mantoux tests in the exposed group is less than in the nonexposed. At the end of thirty months, there are 64 per cent positive reactors in the former group as compared to 40 per cent in the latter. This is probably attributable to the occasional occurrence of natural infection in the exposed group.

All findings thus far reported have comprised results following one vaccination only. Children who were revaccinated were scored only to the time of the second vaccination. In the small group of children who were vaccinated more than once, an interesting finding was noted.

This group comprises only children who failed to develop allergy following the first vaccination.

The findings presented in table 7 indicate that there are apparently some children who cannot be made allergic to Old Tuberculin despite repeated vaccinations with BCG. A satisfactory explanation of this phenomenon cannot be offered.

TABLE 7  
*Study of allergy following revaccination with BCG in children who did not develop allergy following the first vaccination*

METHOD	FOLLOWING 1ST REVACCINATION		FOLLOWING 2ND REVACCINATION		FOLLOWING 3RD REVACCINATION		FOLLOWING 4TH REVACCINATION	
	Num-ber of cases	Positive Mantoux reaction	Num-ber of cases	Positive Mantoux reaction	Num-ber of cases	Positive Mantoux reaction	Num-ber of cases	Positive Mantoux reaction
Intracutaneous.....	26	11 (42%)	10	1 (10%)	2	0 (0%)	1	0 (0%)
Subcutaneous.....	13	3 (23%)	7	1 (14%)		(0%)		(0%)

#### SUMMARY

1. A report of the development of allergy to Old Tuberculin (0.1 and 0.2 mgm.) in 292 intracutaneously and 41 subcutaneously vaccinated children is presented.
2. Relatively more of the intracutaneous group developed a positive Mantoux reaction than of the subcutaneous group, 80 per cent and 62 per cent respectively.
3. Allergy developed sooner in the intracutaneous than in the subcutaneous cases. The highest incidence of allergy in both groups occurred at the end of the sixth month.
4. The percentage of positive Mantoux reactors at the end of the first year following vaccination was 75 per cent in the intracutaneous group, and 50 per cent in the subcutaneous group; at the end of the second year, 45 per cent and 36 per cent; at the end of the third year, 42 per cent and 30 per cent.
5. In the intracutaneous group, a 0.15 mgm. dose produced a greater incidence of allergy than smaller doses. Larger doses showed no advantage over the 0.15 mgm. dose. In a small dose range used for subcutaneous vaccination, no effect upon the incidence of allergy was noted. Two cases with 0.05 mgm. doses both developed a positive Mantoux reaction, but such doses have the undesirable feature of producing local cold abscesses.

## S

- Salicylate, action in tubercle bacilli, 69 705-709  
 Salizid® *See* Isonicotinyl salicylidene hydrazine  
 Salpingitis, tuberculous, in pregnant patient, causing acute hematogenous tuberculosis, (case reports) 68 253-262  
 Sanatorium for tuberculosis, pericarditis in, 76 636-642  
 San Joaquin County (California), mass survey of prisoners, 73 882-891  
 Sarcoidosis, 61 299-322, 62 403-407, (correspondence) 75 852-855  
   BCG vaccination in, 62 408-417  
   and beryllium poisoning, 74 885-897  
   Boeck's sarcoid, 61 730-734, 62 231-285  
   cardiopulmonary function in, cortisone in, 67 154-172  
   cytolysis test *in vitro*, 63 672-673  
   etiology, secondary factors in, (Notes) 71 459-461  
   failure to develop, after oral ingestion of pine pollen, (correspondence) 80 760  
   geographic distribution, (Notes) 70 899-900  
   ineffectiveness of isoniazid-isoniazid in, (Notes) 67 671-673  
   lupus erythematosus cells in, (correspondence) 74 811  
   in lymph nodes, effect on tubercle bacilli of products of, 61 730-734  
   and panarteritis, (case reports) 60 236-248  
   with periarteritis, (case reports) 60 236-248  
   and pregnancy, (case reports) 63 603-607  
   prognosis, 65 78-83  
   pulmonary, evolution of, (case reports) 80 71-77  
   reproduction of, in guinea pigs, with injected material, (case reports) 60 236-248  
   with terminal hypertension, (case reports) 60 236-248  
   transition from open pulmonary tuberculosis to, (case reports) 78 769-772  
   with uremia, (case reports) 60 236-248  
 Sarcoma *See* Tumors  
 Scalene node(s)  
   biopsy, 68 505-522, 76 1002-1006  
   for diagnosis of histoplasmosis, (case reports) 66 497-500  
   in patients with pulmonary calcifications, 72 91-97  
 Scalene lymphadenopathy, postmortem study, (Notes) 76 503-505  
 Schistosomiasis, pulmonary, chronic, 79 119-133  
 School(s)  
   medical, teaching of tuberculosis in, 63 365-371  
   roentgenograms in, 60 501-513  
   tuberculosis case-finding in, 80 (Supplement, October 73-93)  
 Sclerosis, multiple, isoniazid in, 70 577-592  
 Scotland, tuberculosis findings in Edinburgh, 1954-1955, 77 623-643  
 Scotochromogens, source of, (correspondence) 80 277-278  
 Seed plants, antibacterial substances active against tubercle bacilli in, 62 475-480  
 Segments, pulmonary, anatomic distribution of, 60 699-705  
 Selective Service, tuberculosis among registrants in, 60 773-787  
 Self-inoculation, of *M. tuberculosis* and *Ps. aeruginosa* by a diabetic woman, (case reports) 69 818-823  
 Sensitivity  
   to histoplasmin, (correspondence) 61 269  
   to tuberculin  
     attempt to transfer with granulocytes, 64 516-519  
     in Minnesota students, 75 442-460  
 Sensitization, lack of, to PPD-S, 62 77-86  
 Septicemia, tuberculous, fulminant, 59 311-316  
 Serosal surfaces, tuberculosis of, 61 845-861  
 Serologic tests *See* Tests  
 Serology  
   in relationship of modified sheep and human erythrocytes, 79 622-630  
   of tuberculosis  
     leukocyte lysis related to, 69 1002-1015  
     pulmonary, 68 739-745  
 Serum *See also* Blood, Serology  
   albumin, interference with inhibitory action of Tween® on D-29 mycobacteriophage, (Notes) 80 443-444  
   antimycobacterial, antigenicity of, 79 631-640  
   concentrations  
     of amphotericin-B in man, (Notes) 77 1023-1025  
     of glycoprotein, in tuberculous guinea pigs, 68 594-602  
     of isoniazid in tuberculous patients  
       effect of amines on, (Notes) 76 152-158  
       on isoniazid therapy, (Notes) 68 286-289  
     with PAS tablets, (Notes) 77 184-188  
   detection of antibodies in tuberculous patients, 77 462-472  
   enzymes, in pyrazinamide hepatitis, 80 855-865  
   lipase, studies on, (Notes) 78 117-120  
   methylene blue reduction time, tuberculosis influence on, (Notes) 70 907-909  
   microbiologic assay technique  
     for isoniazid metabolism, (Notes) 75 995-998  
     for measuring low concentrations of isoniazid, (Notes) 75 992-994  
   mucoprotein, in patients on linconstarch therapy, (Notes) 78 131-134  
   mycobacteriophage-inhibiting factor in, 80 12-18  
   polysaccharide(s) *See* Polysaccharides

# TREATMENT OF PULMONARY TUBERCULOSIS WITH GOLD SODIUM THIOSULPHATE<sup>1, 2</sup>

MELVIN TESS

During the past twelve years since Møllgaard (1) published the results of his study of sanocrysin (gold-sodium-thiosulphate) and made claims that the substance has a specifically curative effect in tuberculosis, there have been hundreds of men who have tried the drug on patients and reported their results. However, there is still no uniform opinion as to its place as a therapeutic agent. Most of the writers in foreign countries, but not all by any means, report good results and advocate its continued use, some advocating it along with other treatment, while others rely upon it solely, combined with bed-rest. The writer received the impression that in the United States the predominant opinion is that gold is of little or no use (2) (3). Since there are many who have derived unquestionably good results and since we cannot accurately compare clinical records and statistics of any two writers, because each has his individual method of interpreting results, it appears that work with sanocrysin will continue for some time before universal agreement as to its merits can be determined.

An exhaustive review of the literature for this type of a report is obviously unnecessary. However, it was thought practical to mention some of the fundamental facts that have been observed by others and have been the grounds for much discussion.

Møllgaard believed that sanocrysin, introduced into the bloodstream, permeates tuberculous lesions and there kills many, if not all, offending bacilli. The resulting reactions were interpreted as being due to the liberation of toxins from the bacilli, that is, a tuberculin-like reaction. To offset these reactions, he prepared and administered, at the first sign of a reaction, an antiserum obtained from horses which had been injected with "defatted" formalin-treated bacilli. Some men insist that this antiserum must be given, and that the cause of so many unfavorable

<sup>1</sup> From the Robert Koch Hospital, St. Louis Municipal Tuberculosis Sanitarium, Koch, Missouri.

<sup>2</sup> Read before the Trudeau Club of St. Louis, St. Louis, Missouri, May 7, 1936.

*Sputum, cont*

- toxicity of digestants for tubercle bacilli, 60 628-633
- tubercle bacilli in, effect of alcohols on, 68 419-424
- tuberculous
  - decontamination of, by penicillin, (Notes) 67 530-534
  - filtration by membrane filter, (Notes) 77 1019-1022
  - viscous, homogenization of, (Notes) 80 914
- Staphylococcal infection, enhancement with extraction methods, (Notes) 77 1026-1029
- Starch gels, zone electrophoresis in, (Notes) 78 932-933
- Steatorrhea, and tuberculosis (probable), with hypogammaglobulinemia, (case reports) 74 773-782
- Stenosis
  - bronchial, 62 (Supplement, July 80-89)
  - mitral, pulmonary function studies in, 79 265-272
- Sterility, female, caused by tuberculosis, (editorials) 70 1096-1098
- Sterilization, ultraviolet, H<sub>1</sub> Intensity, (Notes) 71 457-458
- Steroids *See* Hormones
- STH *See* Hormones, somatotrophic
- Stilbamidine-PAS-streptomycin, in pulmonary tuberculosis and systemic blastomycosis, (case reports) 68 615-621
- Stomach, tuberculosis of, 61 116-130
- Strains, atypical, growth rates of, in biochemical studies, (Notes) 79 94-96
- Streptococcus faecalis* as cause of pyogenic meningitis, 62 441-445
- Streptodornase-streptokinase *See* Streptokinase-streptodornase
- Streptokinase-streptodornase
  - in extrapleural hematoma, complicating extrapleural pneumothorax, 63 547-555
  - in extrapleural suppurative tuberculosis, 71 1-11
  - in tuberculous and bacterial meningitis, 71 12-29
- Streptomycin *See also* Dihydrostreptomycin
  - activity
    - on H37Rv strain of *M. tuberculosis*, 59 461-465
    - singly and in combination with isoniazid, 67 808-827
    - on tubercle bacilli, 62 582-585
  - bactericidal action on extracellular and intracellular tubercle bacilli, 67 322-340
  - cortisone, in experimental tuberculosis in albino rats, 65 596-602
  - dependent strains of *M. tuberculosis*, (correspondence) 59 219-220
  - dependent tubercle bacilli, 64 192-196
    - pathogenicity of, 63 96-99
  - in development of atypical variants of *M. tuberculosis in vitro*, (Notes) 78 921-926
  - dihydrostreptomycin, toxicity of, 60 564-575
  - effect
    - on bacterial resistance to isoniazid, 67 553-567
    - on bronchocavitary junction in relation to healing, 67 173-200
    - on morphology of tuberculous lesion, 61 525-536
    - on pathology of tuberculous meningitis, 61 171-184
    - on tubercle bacilli
      - electron-microscopy study, 70 328-333
      - in vitro*, 71 556-565
      - in vivo* and *in vitro*, on streptomycin-resistant tubercle bacilli, 66 486-496
  - and enzymatic reactions of *M. tuberculosis*, 65 722-734
  - in esophago cutaneous fistula, 59 687-691
  - in experimental tuberculous meningitis, 70 714-727
  - in guinea pigs with discrete chronic tuberculous lesions, 66 194-212
  - histopathologic changes in lungs after, 61 543-555
  - historical aspects of its development as a chemotherapeutic agent in tuberculosis, 69 859-868
  - historical notes on, 70 9-14
  - inhibition of growth of *M. smegmatis*, 71 743-752
  - intermittent regimens
    - analysis of 97 patients with pulmonary tuberculosis treated with 1 or 2 grams every third day, 63 275-294
    - comparison with daily dosage schedules in the treatment of pulmonary tuberculosis, 63 295-311
    - and PAS in treatment of pulmonary tuberculosis, 63 295-311
- isoniazid
  - action of *M. tuberculosis* within phagocytes, (Notes) 65 775-776
  - compared with isoniazid and streptomycin-PAS in pulmonary tuberculosis, (Notes) 66 632-635, (Notes) 67 108-113, 539-543
  - effect on course of tuberculosis in rabbit eye, 69 1016-1021
  - in experimental tuberculosis
    - in guinea pigs, 68 575-582
    - of mice, antagonism of, (Notes) 68 277-279
  - in fatal meningitis, (case reports) 72 633-638
  - in murine leprosy, (Notes) 72 846-850



mgm. and gradually increase to a maximum single dose between 500 and 750 mgm. The sum of all the gold given varies between 6 and 9 grams.

Some of the results often observed are a drop in temperature, rather gradual (over several months duration), and often to normal. This, of course, is absent in a chronic group of patients (such as ours was) because the temperature usually approaches normal. If the dosage is not too large and no gastrointestinal involvement exists, the appetite is often stimulated and the patient gains weight.

As the lesion in the lung forms scar tissue, the sputum decreases markedly in amount. Various writers report the disappearance of tubercle bacilli from the sputum in as high as 50 to 75 per cent.

The blood examination done by many shows a return of the sedimentation rate to normal and a differential count that approaches normal. A substantial increase in monocytes is observed by some men, being interpreted as a stimulation of the reticuloendothelial system (4) (6).

The subjective feeling of well-being is also described by many. It is only natural to expect such an occurrence with the disappearance of toxicity.

The complications encountered are chiefly those of heavy-metal poisoning. Nausea and vomiting are about as frequent as seen in cases receiving salvarsan. The severity and duration varies with the individual. A certain number cannot tolerate gold at all and in them the injections must be decreased or stopped entirely. One must be careful to give the gold on an empty stomach and caution the patient to eat lightly at the following meal. Along with these complaints occur chilly sensations and rise in temperature. Such symptoms rarely persist over twelve to twenty-four hours. Albuminuria of moderate degree may be observed frequently. Treatment need not be stopped for this, but large amounts of albumin require immediate discontinuation of gold. Skin eruptions, usually of a mild degree, occur in individuals sensitive to gold. These may go on to an exfoliative dermatitis and death. It is well to discontinue gold in the presence of a dermatitis, at least for a time, and if return to gold is advisable, do so cautiously with small doses. Icterus caused by liver damage is a rarer complication and accompanied by death in many cases. Stomatitis with ulcerative lesions and salivation may be encountered. Aching in the limbs and joints, usually transient, occurs at times. In fact, all complications seen from heavy metals may be manifested by gold.

An excitation of the lesion with a definite spread by X-ray and physical

*Streptomycin, cont*

- pulmonary, (Notes) 73 117-122
  - compared with dihydrostreptomycin, 68 229-237, 238-248
  - first clinical trial, (case reports) 71 752-754
  - five-year outcome, 71 193-200
  - follow-up study on, 62 563-571
  - hematogenous, cardiopulmonary function of patients, 64 583-601
  - hypopotassemia and hyponatremia during treatment, 66 357-363
  - once weekly, 69 980-990
  - and other therapy, (editorials) 60 264-268
  - research project, 59 140-167
  - tracheobronchial, 60 32-38
- in tuberculous empyema, drug concentrations attained with various vehicles, 66 271-284
  - cellugel as vehicle, 66 285-291
- in tuberculous enterocolitis, 60 576-588, (case reports) 648-653
- in tuberculous meningitis, 61 247-256, 62 586-593, 67 613-628
- tuberculous patients  $2\frac{1}{2}$  years after, 61 868-874
- in tuberculous pericarditis, 59 656-663
- viomycin, isoniazid, and streptomycyclidene isonicotinyl hydrazine in experimental mouse tuberculosis, (Notes) 68 292-294
- Streptomycyclidene isonicotinyl hydrazine
  - streptomycin, viomycin, and isoniazid in experimental mouse tuberculosis, 68 292-294
  - sulfate, in pulmonary tuberculosis, 70 701-713
- Streptovaricin
  - alone
    - in humans, (Notes) 75 659-666
  - in tuberculosis
    - experimental, (Notes) 75 659-666
    - pulmonary, (Notes) 80 426-430
  - discovery and biologic activity, 75 576-583
  - in experimental tuberculosis, 77 976-982
  - isolation and properties, 75 584-587
  - isoniazid
    - controlled clinical trial, (Notes) 80 757-759
    - in experimental tuberculosis, (Notes) 75 659-666
  - in humans, (Notes) 75 659-666
  - in pulmonary tuberculosis, (Notes) 80 424-425, 431-433
  - in murine leprosy, (Notes) 79 673-676
  - in vivo studies in the tuberculous mouse, 75 588-593
- Stress
  - relationship with adrenocortical function and tuberculosis, 69 351-369
  - request for reprints on adaptive hormones and, (correspondence) 67 677-678
- Students
  - medical and nursing, tuberculosis in, 63 332-338
  - tuberculosis in, (Notes) 76 308-314
- Su 1906, activity on chromogenic mycobacteria, 77 694-702
- Su 3068
  - activity on chromogenic mycobacteria, 77 694-702
  - antituberculosis activities of, 77 703-711
- Su 3912
  - activity on chromogenic mycobacteria, 77 694-702
  - antituberculosis activities of, 77 703-711
- Sulfaguanidine, activity on H37Rv strain of *M. tuberculosis*, 59 461-465
- Sulfathiazole
  - activity on H37v strain of *M. tuberculosis*, 59 461-465
  - in prevention of streptomycin resistance in *M. avium*, (Notes) 76 301-307
- Sulphydryl compounds, effect on growth of tubercle bacilli, 74 42-49
- Sulfone(s) *See also* individual names of drugs, e.g., Glucosulfone, Sulfoxone
  - in experimental tuberculosis, 60 62-77
  - pharmacologic studies, 60 62-77
  - streptomycin in experimental tuberculosis of guinea pigs, 64 102-112
- Sulfoxone, activity on H37Rv strain of *M. tuberculosis*, 59 461-465
- Sulfur hexafluoride, in pneumoperitoneum, 76 1063-1070
- Sulphetrone, clinical toxicity of, 62 160-169
- Surface plate counts, in enumeration of viable tubercle bacilli, 64 353-380
- Surgery *See also* specific surgical procedures
  - in bronchiectasis, cardiopulmonary function before and after, 69 869-914
  - of chest
    - electrocardiographic changes after, 59 128-139
    - peptic ulceration after, 74 358-366
  - in emphysema
    - diffuse, obstructive, 80 825-832
    - pulmonary, 73 191-218
  - indications, in pulmonary tuberculosis, 73 191-218
  - pulmonary *See also* specific procedures
    - Horner's syndrome after, 67 91-100
    - in lupus erythematosus, (case reports) 77 338-345
  - in pulmonary tuberculosis, 73 690-703
    - comparison with roentgenographic findings, (Notes) 71 452-456
    - relationship to chemotherapy, bacteriologic status, and pathology, 80 (Supplement, October 95-115)
  - refusal among tuberculosis patients of, 77 311-322

*Surgery, cont*

- reporting of, (correspondence) 79 679-680
- in spontaneous hemopneumothorax, 71 30-48
- of subpleural blebs, 79 577-590
- thoracic *See also* specific procedures
  - electrocardiographic changes after, 61 50-63
  - major, for tuberculosis, full-term delivery following, 78 697-711
- total statistics, in pulmonary tuberculosis, 68 874-881
- transthoracic, removal of lymph node, causing hemoptysis, (case reports) 65 206-209
- Survey(s) *See also* Case finding, Roentgenography
  - cancer detected in, 62 491-500
  - chest, in tuberculosis, 65 151-154
  - fluoroscopic, in China, 72 356-366
  - international, of pulmonary tuberculosis, (Notes) 73 128-133
- mass
  - in case finding, 59 494-510
  - for pulmonary neoplasms, 62 501-511
  - X-ray, what's wrong with, (correspondence) 60 532-535
- roentgenographic
  - lesions undetected in, 64 249-255
  - on private patients, (correspondence) 66 502
  - in schools and industries in San Antonio (Texas), 60 501-513
  - in small hospitals, (editorials) 64 313-317
  - in Washington (D C ), 1948, 66 548-566
- tuberculin patch test among school-age children in Liberia, (Notes) 67 665-668
- Suture, ligation, and partial thoracoplasty in pulmonary tuberculosis, 70 61-70
- S waves, prominent, electrocardiograms with, 62 307-313
- Sweden, BCG vaccination in, (correspondence) 79 678-681
- Symphysis, guided, 66 134-150
- Symposium on emphysema and the "chronic bronchitis" syndrome, Aspen (Colorado), June 13-15, 1958, 80 (Supplement, July 1-213)
- Symptoms, cardiac, in tuberculous patient, 62 (Supplement, July 98-103)

**T**

- Taurine, in experimental tuberculosis, (Notes) 74 638-640
- Teeth, restorations (fillings), effect of PAS on, (Notes) 68 622-624
- Temperature-influenced mycobacteria, in mice and in chick embryo, 73 650-673
- Terramycin® *See* Oxytetracycline
- Test(s)
  - drug-susceptibility, in tuberculosis, (Notes) 77 350-355, (Notes) 78 111-116

## gel

- diffusion, in tuberculosis, 80 886-894
- double diffusion, in tuberculosis, 80 153-166
- Histoplasma capsulatum* and *Blastomyces dermatitidis* polysaccharide skin, on humans, (Notes) 80 261-266
- intracisternal, of bacillary virulence, 76 426-434
- maximal expiratory flow, for detecting ventilatory obstruction, 78 180-190
- microcolonial, for virulent mycobacteria, (correspondence) 73 600-601
- mouse, for pulmonary tuberculosis, (Notes) 77 1005-1011, 1012-1016
- neotetrazolium inhibition, 77 662-668
- niacin
  - in differentiation of tubercle bacilli, (Notes) 79 810-812
  - in distinguishing mycobacteria, (Notes) 79 663-665
- oxidation-reduction dye, modification of, for determination of virulence
  - of *mycobacteria in vitro*, (Notes) 66 99
- oximeter, in emphysema, diagnosis of, 80 705-715
- pulmonary function *See* Pulmonary function of respiratory function, 79 457-467
  - using direct-writing ear oximeter, 74 511-532
- serologic
  - for tuberculosis
    - absorption in, (Notes) 66 762-764
    - new, 64 675-681
- simple paper strip urine, for PAS, (Notes) 80 585-586
- skin, simultaneous, effect on size of tuberculin reactions, 65 201-205
- tuberculin
  - disc-method, 77 778-788
  - patch, among Liberian school-age children, (Notes) 67 665-668
- urine
  - for detection of isoniazid, (Notes) 80 904-908
  - for detection of PAS in ambulatory tuberculous patients, (Notes) 79 672
- of ventilatory capacity
  - index of expiratory force in, 78 692-696
  - maximal minute expiratory flow, 72 783-800
- Testosterone *See* Hormones
- Tetracycline
  - antituberculosis activity, 72 367-372
  - influence on antibodies in ornithosis, 74 566-571
- Therapeutic Trials Committee of the Swedish National Association Against Tuberculosis PAS treatment in pulmonary tuberculosis, comparison between 91 treated and 82 untreated cases, 61 597-612
- Therapy
  - with paired combinations of antituberculosis drugs, 80 627-640

*Therapy, et*

- of peripheral tuberculous lymphadenitis, 68 157-161
- physical, post thoracoplasty, 60 189-205
- Thiazolidinone *See* Su 3912
- Thiazoline *See* Su 306S
- Thiazolsulfone
  - factors determining adequate dosage of, 62 61S-631
  - in meningeal tuberculosis, in children, 61 159-170
  - streptomycin,
    - iniliary tuberculosis, in children, 61 159-170
    - in pulmonary tuberculosis, in infants, 61 717-750
- Thiocarbandin
  - antituberculosis activity *in vitro* and in experimental animal, 78 570-575
  - effect on *M. tuberculosis* *in vitro* and *in vivo*, 77 301-310
  - isoniazid, in pulmonary tuberculosis, (Notes) 80 590-593
- Thiocarbamide(s) *See also* Su 1906
  - antituberculosis activity of, in mice, 77 301-310
  - in pulmonary tuberculosis, (Notes) 74 468-470
- Thioethyl compounds, antituberculosis activity of, 74 59-67
  - effect of ventilation on, 74 6S-71
  - metabolic cleavage of, 74 78-83
- Thioglycollate medium for differentiating mycobacteria, (Notes) 77 356-35S
- Thiosemicarbazone(s)
  - amithiozone
    - carbohydrate metabolism associated with, (case reports) 66 373-377
    - causing agranulocytosis, (case reports) 65 339-343
    - resistance and action in mycobacteria, mechanism of, 80 559-568
    - in selected tuberculous pulmonary lesions, 65 692-703
    - susceptibility of tubercle bacilli to, 63 487-489
    - method for determining, 62 638-644
    - tests for, 62 638-644
  - toxicity,
    - in dogs, 64 659-668
    - hepatic, 64 159-169
  - in tuberculosis
    - experimental, in guinea pigs, effect of in combination with dihydrostreptomycin as compared with PAS-dihydrostreptomycin, 63 339-345
    - pulmonary, 64 170-181
  - antituberculosis activity of, 61 1-7, 8-19
  - chemical studies, 61 1-7
  - 4-acetylaminobenzal
    - in experimental tuberculosis in guinea pigs, 62 144-148
    - effect of, in combination with dihydrostreptomycin as compared with PAS-dihydrostreptomycin, 63 339-345
  - human pharmacology, 62 128-143
  - p* acetylaminobenzaldehyde, susceptibility of tubercle bacilli to, 63 487-489
  - p* ethylsulfonyl benzaldehyde (Berculon B) in humans, 68 400-410
  - p* isobutoxybenzaldehyde, failure as anti-tuberculosis drug in man, (Notes) 68 791-793, 791-795, 796-798, 799-802
- Tibione® *See* amithiozone, above
- in tuberculosis,
  - chemotherapy, 61 20-38
  - experimental, in mice, (correspondence) 60 539
  - in humans, 61 145-157
- Thiourea, substituted
  - antituberculosis activity, 70 121-129, 130-138
  - in experimental tuberculosis
    - in guinea pigs, 70 130-138
    - in mice, 70 121-129
- Thoracic surgery *See* Surgery, *also* names of specific procedures
- Thoracoplasty
  - bronchspirometry before and after, 75 724-729
  - contralateral rib fractures during, (case reports) 66 233-239
  - deformities, prevention of, 66 436-448
  - disappearance of tubercle bacilli in sputum after, 64 307-312
  - effect of penicillin on wound infection after, 61 346-352
  - failure as indication for resection, 62 434-438
  - gelatin foam in, 61 193-200
  - homolateral, effect of paralyzed hemidiaphragm on, 60 183-188
  - late results after, 59 113-127
  - partial, and suture ligation, in pulmonary tuberculosis, 70 61-70
  - patients, postoperative management of, 61 57-59
  - post-thoracoplasty, physical therapy in, 60 189-205
  - primary, for pulmonary tuberculosis, 78 832-838
  - in pulmonary tuberculosis, 59 113-127, 60 273-287
  - in relation to type of lesion, 60 273-287
  - resection after, 60 406-418
    - pre- and post-, in tuberculosis, 79 204-211
    - pulmonary, simultaneously in pulmonary tuberculosis, 65 159-167
  - results
    - according to type of pulmonary tuberculosis, 62 645-653, 69 930-939
    - necessity for accurate evaluation of, (editorials) 60 383
  - ribs as possible source of homogenous bone grafts, 63 210-212

*Thoracopneumy cent*

- spread or exacerbation of pulmonary tuberculous lesions as result of, 61 648-661
- in tuberculous empyema, 66 522-533
- ventilatory function tests in evaluating patients for, 63 76-80

## Thoracoscopy, 59 210-238

- Thoracotomy, diagnostic, in idiopathic pleural effusion, 71 954-957

## Thorax

- removal of calcified lymph node, (case reports) 65 206-209

- surgery of, bronchspirometry in, 75 730-744
- vertical tomography of, 62 170-175

- Thromboecytopenic purpura, and bronchogenic carcinoma, (case reports) 67 509-513

- Thromboembolism, incidence and significance of, in pulmonary tuberculosis, 61 826-834

- Thrombosis of cerebral vessels with necrosis of the basal nuclei, 61 247-256

Thymoma *See* Tumors

## Thyroid

- function, in patients treated with isoniazid-PAS, 80 845-848

- isoniazid action against, (Notes) 71 889-891

- PAS action against, (Notes) 71 889-891

- in tuberculosis, native resistance to hyperthyroidism in, 79 152-179

- hypothyroidism, 79 180-203

- Time factor, in studies of outcome of chronic disease, (editorials) 63 608-612

## Tissue(s)

- acids, fatty, in resistance of tubercle bacilli in rabbits, 69 710-723

- animal, tuberculostatic agent present in, (Notes) 63 119

## cultures

- mammalian cells and mycobacteria in, (correspondence) 75 347-348

- mycobacteria in, 77 789-801

- studies on resistance in tuberculosis, 79 221-231

- tuberculin reaction in glucose in, 78 712-724

- internal, allergy of, effect of estrogen on, 59 186-197

- mycobacteria in, retention and differentiation of, 74 608-615

## tuberculous

- granulation, distribution of iron in, 61 560-562
- tubercle bacilli in, (correspondence) 75 519-520

## Tomography

- and bronchography, in apical bronchiectasis, 74 388-399

- vertical, of the thorax, 62 170-175

- Tongue, nicotinamide therapy of changes in, 62 360-373

- Tonsils, faucial, primary tuberculosis of, (case reports) 69 612-617

## Torsion, splenic, 62 139-140

- and pneumoperitoneum, 70 166-170, (correspondence) 70 923

## Trachea

- anomalous bronchus to the right upper lobe, (case reports) 64 686-690

## fenestration

- evolution and early results of, 79 773-779
- in exploration of bronchial tree, 78 815-821
- in pulmonary diseases, 78 815-821

- papillomatosis of, (case reports) 71 429-436

## reconstruction

- plastic, 64 177-188

- surgical, 62 176-189

- tuberculosis, 60 604-620

## Tranquilizer(s)

## effect

- on activity of ambulatory tuberculous patients, (Notes) 79 531-532

- on hospitalized tuberculous patients, (Notes) 78 127-130

- Transaminase, glutamic oxalacetic and pyruvic, in pulmonary tuberculosis, (Notes) 79 251-252

- Trauma, of lung, at pneumothorax induction, 60 557-563

- Treatment failures, (correspondence) 79 105

- Tributyrylase and fatty acids in BCG rabbits, 72 340-344

- 3,3',5-Triiodo L-thyronine in tuberculosis and pneumococcosis, survival time of mice with, 79 339-343

- Triiodothyronine and propyl thiouracil in experimental tuberculosis, (Notes) 73 434-437

- Trisodium phosphate transport-digestion method for processing sputum and gastric specimens, (Notes) 70 363-366

## Triton A-20

- antituberculosis activity of, in mice, 65 718-721

- 1,4-dimethyl-8-isopropyl-bicyclo-decapentane therapeutic activity in experimental tuberculosis and leprosy, (Notes) 75 684-687

- effect on streptomycin susceptibility of resistant strain of *M. tuberculosis*, 62 91-98

- Triton WR 1339 *See also* Polyoxyethylene ether and malachite green in charcoal media for tubercle bacilli, (Notes) 71 894-897

- in murine leprosy, (correspondence) 76 915-916

- Trudeau *See also* American Trudeau Society Foundation, Edward L., inauguration of, 62 (Supplement, July 104-113)

- Sanatorium, closing, (editorials) 71 163-164

- School of Tuberculosis, inauguration of, 62 (Supplement, July 104-119)

- Trypsin, effect on *M. tuberculosis in vitro*, 76 279-285
- Tubercle bacillus(1) *See also Mycobacterium tuberculosis*
- acid-fast
- microorganisms other than, in HeLa cells, growth characteristics of, (Notes) 80 744-746
  - wild-type, titration of cord formation as measure of pathogenicity, (Notes) 78 799-801
- activity of streptomycin-PAS on, 59 554-561
- air-borne, isolation of, in a tuberculosis hospital, (Notes) 67 878-880
- amithiozone susceptibility, 63 487-489
- antibacterial substances in seed plants active against, 62 475-480
- antibodies against hemagglutination test for, 63 667-671
- artificial cellular immunity against, 69 690-704
- atypical, pulmonary disease from, (case reports) 80 738-743
- autolysis and growth of two strains, 65 75-82
- avian, characteristics and resistance of, 76 435-450
- in bone marrow, 63 346-354
- bovine
- effect of calf lung fatty acids on, 75 630-637
  - virulence for rabbit, (Notes) 67 265-266
- catalase activity, (Notes) 73 768-772, 76 1007-1015
- and virulence, 78 735-748
- catalase-positive and -negative, 74 42-49
- centrifugation for concentrating, (Notes) 76 899-901
- charcoal diluent for, 70 989-994
- counting chambers for, (correspondence) 70 376-377
- cultures
- "bluing" phenomenon as contamination source, (Notes) 80 95-99
  - direct, in patient's blood, as drug therapy test, (Notes) 80 85-88
  - filter paper technique for early detection of microcolonies, (Notes) 70 916-919
- media
- blood, 64 551-556
  - charcoal, 70 955-976
  - Triton WR 1339 and malachite green in, (Notes) 71 894-897
  - comparison of, 63 459-469, 470-475
  - in egg, (Notes) 73 139-141
  - egg yolk, 70 977-988
  - negative, procedure for, (correspondence) 68 470-471
  - neotetrazolium chloride in (Notes) 68 625-628
  - by test tube or bottle, (correspondence) 77 1030-1031
- cycloserine effect, (Notes) 72 685-686
- cytology, phase contrast studies in, (Notes) 73 294
- detection
- by egg embryo procedure, (Notes) 76 315-319
  - of small numbers
  - concentrating agents' lethal action on, 69 991-1001
  - from dispersed cultures, using mice, guinea pigs, and artificial media, 65 572-588
- differentiation of human from atypical acid-fast, (Notes) 79 810-812
- dihydrostreptomycin-resistant, enhancement of, 63 568-578
- dissemination of, in experimental tuberculosis in the guinea pig, 61 399-406
- dissociation of, 62 (Supplement, July 22-33)
- drug resistant, 67 553-567
- detected in sputum by slide cultures, (Notes) 75 331-337
  - distribution in lung, 73 406-421
  - in pretreatment patients, 72 143-150, 151
  - through prolonged chemotherapy, (Notes) 76 871-876
- effect
- of I<sup>131</sup>, radioactive, -labeled 3,5-diiodo PAS *in vitro* on, 65 316-324
  - on migration of phagocytes *in vitro*, 59 562-566
  - of neomycin on, 62 300-306
  - of quartz on recoverability, from resected pulmonary lesions, (Notes) 71 308-313
  - sarcoid lymph node products on, 61 730-734
  - enzymatic digestion and concentration, (Notes) 76 896
- extracellular and intracellular, bactericidal action of isoniazid, streptomycin, and oxytetracycline on, 67 322-340
- extraction
- and fractionation of water soluble components from, 64 602-619
  - of proteins and other constituents from, 61 798-808
- gastric washings for, evaluation of four methods for collecting and mailing, 65 617-626
- growth
- affected by sulphydryl compounds, 74 42-49
  - delayed emergence of, (Notes) 75 506-509
  - failure of chick embryo extract to accelerate, (Notes) 65 783-785
  - inhibited by isoniazid antagonized by ketone compounds, (Notes) 68 273-276
  - measurement, 62 87-90
  - in monocytes from normal and vaccinated rabbits, 69 495-501, (correspondence) 69 1059-1062
  - pattern and virulence of, 65 181-186

*Tubercle bacillus*

- in rabbits given cortisone, (Notes) 77 527-535
- stimulated by deoxyribonucleic acid, 80 845-870
- in Tween' albumin medium
  - B.C.G., 18 312-371
  - strain H37Rv, 68 321-341
- guinea pig virulence of, (Notes) 73 768-772
- hemagglutination reaction slide test modification of, for antibodies against, 63 667-671
- human
  - effect of calf lung fatty acids on, 75 630-637
  - mycobacteriophage (D 29) inhibited in, by serum factor, 80 12-15
  - virulence
    - for guinea pigs 73 261-275
    - for rabbit, (Notes) 67 265-266
- inhalation of, protection against, 59 1-9
- inhibition
  - tested in synthetic organic bases, (Notes) 65 631-634
  - by urine, role of ascorbic acid, 69 405-418
- intracellular
  - acidity of, 74 552-565
  - growth and virulence of, 69 479-494
  - isoniazid action on, 66 125-133
- isolation
  - drug-susceptibility, and catalase testing, from patients treated with isoniazid, 70 852-872
  - from feces and gastric contents of intravenously infected mice, 62 181-183
  - methods, 61 563
  - by microculture method, (Notes) 75 1007-1008
  - from patients treated with streptomycin, 61 705-718
- isoniazid effect
  - on growing and resting, (Notes) 69 125-127
  - lipid, 72 713-717
  - proposed mechanism for, (correspondence) 69 1062-1063
- isoniazid-resistant, 70 91-101, 73 390-405
  - altered growth characteristics of, (Notes) 66 626-628
  - and catalase activity, (Notes) 69 471-472
  - growth requirements, (correspondence) 75 155-156
  - catalase and pathogenicity, 70 641-664
  - metabolism, 71 785-798
  - pathogenicity
    - in children, 74 (Supplement, August 75-89)
    - human, 71 390-405
  - pathology of lesions caused by, (Notes) 74 633-637
  - strains infecting children, 80 326-339
  - superinfection with, (case reports) 77 168-171
  - susceptibility to pyrazinamide, (Notes) 72 810-842
  - virulence, 68 545-556, 70 728-733, (correspondence) 70 375-376
    - in guinea pigs and mice, (Notes) 69 464-468
- isoniazid-streptomycin action *in vitro*, 71 556-565
- isoniazid susceptibility, (Notes) 73 768-772
- logie acid as inhibitor of, 61 738-741
- lipids, 66 28-35
- lipopolysaccharide, reticuloendothelial system response to, 70 703-805
- liquefaction of, mechanism, 63 694-705
- in lungs of rabbits, endocellular proteinases in, 63 694-705
- lysozyme effects, 67 217-231
- metabolism
  - isotopic carbon studies, 71 609-615
  - production of a pharmacologically active metabolite, 63 100-107
  - oxidative, benzoate and salicylate effect, 69 705-709
- methanol extracts, (correspondence) 74 807-808
- immunizing effects on mice, (Notes) 73 781-784
- method
  - for determining susceptibility
    - to amithiozone, 62 638-644
    - to streptomycin, 61 569-577
  - of differentiating from other bacteria, 75 529-537
- in mice, relation between size of infecting dose and survival time, 64 531-540
- microculture method for isolation, (correspondence) 76 159-160
- in mouth wash, membrane filter culture for, 71 371-381
- mutants, isoniazid resistant, 70 465-475
- in necrotic lesions, biology of, (Notes) 66 629-631
- negative cultures for, procedure with, (correspondence) 69 128
- nonpathogenic, viable, in mice, 75 280-294
- nuclei and mitochondria in, 67 59-73
- $P^3$  labeled, virulence of, 79 738-745
- PAS resistant, 75 608-617
  - genetic considerations of mechanisms involved in, (Notes) 79 371-373
- pathogenicity, and isoniazid susceptibility, 68 734-738
- in pathologic specimens, microculture in blood, (correspondence) 73 785-786
- phase contrast and electronmicroscopic studies on effect of PAS, isoniazid, and streptomycin on, (Notes) 73 296-300
- in primary tuberculosis, late discharge of, 79 31
- propagability of, extended incubation on, 77 802-814

*Tubercle bacillus(s), propagability of, cont*

protein, 71 704-721

in pulmonary lesions

isoniazid effect on growth of, (Notes) 79 518-521

resected, 66 44-51, 74 376-387

"purified way," reticulo-endothelial system response to, 70 793-805

resistance

to benzalkonium chloride, 70 312-319

to chemotherapeutic agents, 61 483

to isoniazid, catalase activity, and guinea pig virulence correlated, (Notes) 72 246-251

to pyrazinamide *in vivo*, 74 572-580

of rabbits, relationship of tissue fatty acids to, 69 710-723

to streptomycin in early tuberculosis of guinea pig, 59 674-678

respiratory quotients, at low oxygen tension, (Notes) 67 669-670

ring method, for study of, (Notes) 77 524-528

and saprophytic mycobacteria, differentiation of, (Notes) 74 958-960

self-injection, (case reports) 60 514-519

slide culture method for detection, 60 51-61

in sputum

disappearance of, following thoracoplasty, 64 307-312

effect of alcohols on, 68 419-424

isolation of, in medium, (Notes) 76 703-705

undigested, penicillin as decontaminant in cultures for, (Notes) 67 530-534

staphylococcal infection-enhancing properties of, methods of extraction effects on, (Notes) 77 1026-1029

streptomycin action on, 62 582-585

streptomycin-dependent, 64 192-196

pathogenicity of, 63 96-99

streptomycin-resistant, 59 391-401, 402-414, 438-448, 61 719-724, (correspondence) 62 227, 345-352

without chemotherapy, 70 637-640

in children with tuberculosis, 66 63-76, 80 326-339

effect of streptomycin on, *in vivo* and *in vitro*, 66 486-496

inoculation in reinfection tuberculosis, 74 258-276

in necropsy specimens, 63 449-458

streptomycin-treated, electronmicroscopy of, 70 328-333

survival, in tuberculous lesions, (Notes) 65 637-640, (correspondence) 66 381-382

susceptibility

to antimicrobials, 76 1031-1048

to streptomycin in early tuberculosis of guinea pigs, 59 664-673

*in vitro*

to pyrazinimide, (Notes) 65 635-636

to streptomycin, 59 336-352

suspensions

dilute, standardization of, 59 325-335

influence of dispersion on virulence, 75 488-494

viability for, test of, (Notes) 66 95-98

toxic lipid component

isolated from petroleum ether extracts of young bacterial cultures, 67 629-643

occurrence

in chloroform extracts of young and older bacterial cultures, 67 828-852

in various bacterial extracts, 67 853-858

toxicity of sputum digestants for, 60 628-638

triton malachite green charcoal agar for detection of, (Notes) 75 338-339

in tuberculous tissue, viable and stainable counts on, (correspondence) 75 519-520

viomycin effect against resistance to certain drugs, 63 36-43

viability

with and without chemotherapy, (Notes) 67 874-877

in embalmed human lung tissues, 59 429-437

enumeration of, 74 84-91

by surface plate counts, 64 353-380

in organs of mice, 76 616-635

quartz dust for challenging, (Notes) 69 841-842

virulent

biochemical analysis, 80 535-542

detection of, when coexisting with attenuated bacilli in the mouse, 70 1053-1063

human

in mice, in assessment of chemotherapeutic activity, 64 541-550

toxic effects of DL serine on, (correspondence) 60 385

influence of "cord factor" in, 77 482-491

influence of cord formation in, 78 83-92

penicillin effect on growth, 80 849-854

in relation to oxidation, 64 520-533

*in vitro* susceptibility in meningeal and milary tuberculosis, 74 (Supplement, August 232-240)*in vivo* multiplication, 75 756-767*in vivo* and *in vitro*, biologic differences in, 75 495-500

washed, formation of tuberculin by, in citrate solution, (Notes) 67 526-529

*in wax*

immunogenicity, 80 216-222

for mouse tuberculosis, 76 752-760



**Tuberculin**

- allergy
  - after BCG vaccination, 70 1064-1082
  - in guinea pigs vaccinated with BCG, 60 547-556
- antigens, with gel-diffusion technique, 75 601-607
- assay in guinea pigs, 59 692-700
- autolytic, transcutaneous tests in children, 60 45-50
- compared in BCG-vaccinated and unvaccinated persons, 70 71-90
- conversion rates in Kansas City as indication of prevalence of infection, 69 227-233
- desensitization, in tuberculous lymphadenitis, (case reports) 60 249-257
- dilutions, instability of, (Notes) 72 126-128, (Notes) 74 297-303
- dose for single test tuberculin testing, 60 483-486
- effect
  - on tissues from tuberculin-sensitized hosts, (Notes) 73 581-585
  - on *in vitro* cytotoxicity of leukocytes, 60 212-222
- formation of, by washed tubercle bacilli in citrate solution, (Notes) 67 526-529
- fractionation, 68 425-438, 439-443
- fractions, 59 86-101
  - effect, on leukocytes from normal and tuberculous animals, 65 250-271
  - purified, from unheated cultures in testing BCG-vaccinated subjects, (Notes) 69 300-303
- for testing BCG subjects, 66 335-344
- hemagglutination procedure in study of, 65 272-277
- hypersensitivity
  - cutaneous, elicited by tuberculin-treated erythrocytes, (Notes) 64 332
  - in man, tissue culture analysis, 72 577-600
  - in pulmonary tuberculosis, (Notes) 74 474
  - transfer, 73 246-250
- induced pneumonia in rabbits, adrenocorticotrophic hormone in, 64 508-515
- inhibition, by antihistaminic drugs and rutin, 59 701-706
- intracutaneous reaction to, topical hydrocortisone acetate ointment at site, (Notes) 79 666-668
- intradermal, reaction on guinea pig, 69 806-817
- intravenous injections, effect on subsequent tuberculin skin reactions in hypersensitive rabbits, 61 556-559
- isolation
  - of polysaccharides from, 59 86-101
  - of proteins from, by alcohol fractionation, 59 86-101
- leukocytic sensitivity to
  - chemotherapy effect on, 77 815-822
  - in guinea pigs, (Notes) 76 888-891
  - negative tuberculosis, 63 501-525, (correspondence) 64 468-469, 469-471
- OT (Old Tuberculin)
  - and paratubercle bacilli products, skin reaction, 79 731-737
  - sensitized sheep and trypsinized human erythrocytes, serologic relation, 79 622-630
- patch, survey among school-age children in Liberia, (Notes) 67 665-668
- PPD, 71 704-721
  - cattle erythrocyte sensitization with, (Notes) 77 177-180
  - compared with new purified protein, 66 345-350
  - delayed skin reactivity to, 80 398-403
  - and other antigens prepared from atypical acid-fast bacilli and *Nocardia asteroides*, 79 284-295
  - prepared by ammonium sulfate precipitation, (correspondence) 74 810-811
  - sensitization with, johnin and tuberculin, (Notes) 77 177-180
  - treatment of tuberculous meningitis in children, 76 832-851
- protein, purified, new
  - comparison with PPD, 66 345-350
  - standardization and stability of, (editorials) 80 255-256
- reaction
  - affected by isoniazid, 74 7-14
  - analysis, 71 49-73
  - and antihistaminics, (editorials) 62 555
  - in children, antihistamine medication on, 60 354-358
  - cytology, in skin windows in man, 69 216-226
  - cytotoxicity of, for sensitized cells, failure to demonstrate *in vitro*, 63 674-678
  - effect
    - of antihistamines on, (correspondence) 60 811, 61 442, 735-737
    - of simultaneous skin tests, 65 201-205
  - fluctuation in different geographic areas and its relationship to resistance, 63 121-139
  - hyperergic reactivity, nonspecific, at site, 69 205-211
  - and isoniazid treatment, 69 733-744
  - specificity, (editorials) 63 355-359
  - stability of, 78 862-870
  - in tissue culture, glucose in, 78 712-724
  - in tuberculous patients, 80 569-574
  - in vaccine assay, 66 351-356
- reactor
  - resistance, (correspondence) 69 846-847
  - treatment, (correspondence) 69 843-844
- sensitivity
  - and adrenocortical function in humans, 73 795-804

*Tuberculin sensitivity test*

- in aged, 75 161-168
- attempt to transfer with granulocytes, 61 516-519
- cellular basis in, 68 716-759
- changes in anergic and partially anergic patients treated with antimicrobial therapy, 67 286-291
- and chemotherapy, in rabbits, 70 329-338
- leukocytic transfer of, 78 316-352
- in Minnesota students, 75 112-160
- nonspecific, 68 678-694
- passive transfer of, 80 398-403
- with pulmonary calcifications, 59 613-619
- in relation to BCG in Hong Kong, 76 215-224
- in relation to tuberculosis morbidity, 76 517-539
- of skin of forearm and shoulder, (Notes) 72 215
- sensitized
  - cells, inhibition of, *in vitro*, 80 410-414
  - guinea pigs, inhibition of leukocyte migration from, 80 19-25
- shock
  - failure of polyoxyethylene ether to protect against in guinea pigs, (Notes) 79 382-383
  - in tuberculous mice, (Notes) 68 629-630
- skin reaction
  - acceleration, 61 556-559
  - for assay of tuberculin in guinea pigs, 59 692-700
  - correlation with pulmonary lesions in BCG-vaccinated and control persons, 68 713-726
  - effect of antihistaminics on, 62 525-531
  - hydrocortisone acetate ointment in, (Notes) 80 587-589
  - pulmonary tuberculosis in, 78 399-402
- skin sensitivity
  - to BCG, duration variation, 60 541-546
  - effect of estrogen on, 59 186-197
  - in old age, 77 323-328
- standardization
  - in humans, 66 292-313
  - lack of sensitization to PPD S, 62 77-86
- test
  - in case finding in a general hospital, pilot study, (Notes) 79 378-381
  - in differential diagnosis of pulmonary lesions, 63 140-149
  - disc method, 77 778-788
  - influenced by BCG vaccination, 72 35-52
  - isoniazid effect, (Notes) 67 535-537
- testing
  - in Honolulu schools, 78 871-883
  - of midshipmen and recruits of the Navy and Marine Corps, 62 518-524
  - in New York City, (Notes) 69 1057-1058

- suitable dose for single test, 60 483-486
- in tuberculosis case finding, 78 667-681
- in tuberculous meningitis, (case reports) 74 277-283

**Tuberculoma**

- of the brain, 62 654-666
- of the cerebellopontine angle simulating acoustic neuroma, (case reports) 63 227-229
- and cystic thymoma, possible confusion between, (case reports) 70 155-160
- of lung, 78 403-410
  - simulating bronchogenic carcinoma, 61 431-435
- of mediastinum, 64 327-352

**Tuberculo protein, in tuberculosis, interference with antibodies, 73 547-562****Tuberculosis See Pneumoconioses****Tuberculosis**

- and abortion, 70 49-60
- abortive, in guinea pigs, induced by pathologic material containing young tubercle bacilli, (correspondence) 68 467-471
- activation during prednisone therapy, (case reports) 76 140-143
- active
  - ambulatory, outside institutions, (correspondence) 76 506-507
  - chemotherapy for, (correspondence) 63 490-492
  - cycloserine-isoniazid in ambulatory treatment, (Notes) 80 89-94
  - in women, food intake of, 60 455-465
- air hygiene in, study in pilot ward, 75 420-431
- alcoholics with, before and during hospitalization, (editorial) 79 659-662
- ambulatory patients with
  - observations on "open-negative" syndrome in, 78 725-734
  - urine test for detection of PAS in, (Notes) 79 672
- in American Negroes, 60 332-342
- in anergic and partially anergic patients treated with antimicrobial therapy, changes in tuberculin sensitivity of, 67 286-291
  - prolongation of life, 67 292-298
- in animals, 77 908-922
- with anorexia, insulin treatment for, 60 25-31
- in anthraco silicosis, 65 24-47
- of appendix, 64 182-191
- arcana of
  - Parts I and II, 78 151-172
  - Part III, 78 426-453
  - Part IV, 78 583-603
- arrested, in women, food intake of, 60 455-465
- ascorbic acid in, 64 381-393
- association, effect of isoniazid on program of, (editorials) 66 615-618

*Tuberculosis cont*

ureomycin in treatment of, 61 875-880

## avian

in chicks, streptomycin and dihydrostreptomycin in, 60 366-376

and silicosis, (case reports) 80 78-81

bacteriologic media, eliminating of precleaning cage laid hens' eggs in preparation of egg fluid for, (Notes) 79 677

bacteriologic specimens, agitator for, (Notes) 70 176-177

bacteriology, benzalkonium chloride in, (Notes) 80 912-913

## BCG produced

fatal, 70 102-112, (correspondence) 71 321-323

biologic aspects, 68 1-8

biopsy, needle, of parietal pleura, 78 17-20 of breast, 72 810-821

bronchial, 60 604-620, 63 381-398

major, streptomycin in, 60 32-38

"quiescent," 73 451-471

and bronchiectasis, relationship between, 61 387-398

## bronchogenic

in dog, 73 748-763

role of lymphatics in development of, 67 440-452

*Candida albicans* in sputum of patients with, (Notes) 77 543-545

care, in countries of limited means, (correspondence) 73 444-445

case finding *See* Case finding, Surveys

caseous pneumonic, isoniazid in, 65 402-428 cavitory

drug-resistant, pulmonary resection of, using ancillary drugs, 79 780-789

of lower lobe, 63 625-643

surgery in, 77 593-604

center for, length of stay in, (Notes) 74 961-963

challenge today of, 78 661-666

## changes

in content of serum polysaccharide during sensitization and development, 62 67-76

as seen by a pathologist (ATS conference paper), 79 684-686

chemoprophylaxis, 80 (Supplement, October 1-21)

immunity and prevention in, (editorials) 74 117-120

chemotherapy, 59 223-239, 61 407-421, 67 680-697, 78 251-258, 79 492-496

with amithiozone, 61 20-38

clinical and histopathologic study, 69 247-260

complicating pneumoconiosis, (correspondence) 79 818

in infants and children, 74 (Supplement, August 225-231)

isoniazid, streptomycin, and PAS in combinations, 32 week observations on, (Notes) 70 521-526

long term, and prognosis in, (correspondence) 70 178

of unhospitalized patients, 70 1012-1052

in childhood, 71 (Supplement, August 1-6), 76 579-587

electrophoretic patterns and hemagglutination reaction, (Notes) 73 964-965

fatal, morphology of, 74 (Supplement, August 7-12)

fever and roentgenographic exacerbations following isoniazid, (case reports) 72 527-536

primary, antimicrobial treatment, (correspondence) 72 398-402

prognosis, 72 513-526

in Puerto Rico, 76 388-397

serum gamma globulin in, 74 15-28

## chronic

experimental, 73 378-389

testosterone in, 70 1020-1029

clinical, neomycin in, 63 427-433

and coccidioidomycosis, 61 887-891

disseminated, 59 415-428

pulmonary, 70 109-120

## contacts

in Edinburgh (1954-1955), 77 623-643

tuberculin sensitivity in, 68 678-694

contamination of eating utensils, (Notes) 74 462-463

## control

among American Negroes, 60 332-342

in hospital personnel, 67 74-84

medical progress in, 70 383-390

program, for student nurses, 73 868-881

and treatment, detention ward in, 74 410-416

in underdeveloped areas, social sciences in, (correspondence) 75 345-346

## corneal

cortisone in, 74 1-6

phase contrast microscopy of, 74 1-6

corticotropin and corticosteroids as adjuvants in, 76 708-710

cortisone and corticotropin in, with and without antimicrobial therapy, 70 623-636

cost, 1956 fiscal estimate, (Notes) 77 172-176

## cutaneous

in children, 74 (Supplement, August 160-169)

inoculation causing, 63 526-537

cyanacetic acid hydrazide in, 74 417-427

cycloserine and isoniazid in, 75 553-575

deaths *See* Tuberculosis, mortality

*Tuberculosis, cont*

- in diabetics, 65 (Supplement, January 1-50),  
76 1016-1030, 77 990-998
- surgery for, 74 747-756
- diagnosis, bacteriologic, 59 589-598, (correspondence) 76 1110-1111
- DIAGNOSTIC STANDARDS of (NTA, 1950), (correspondence) 74 158-159
- discharges
  - irregular, 71 419-428
  - from a hospital, 68 393-399
- drug-arrested, reinfection in guinea pigs with,  
80 554-558
- drug-susceptibility tests in, (Notes) 77 350-355
- effects of amines on serum concentrations of  
isoniazid in patients with, 76 152-158
- elimination of, as public health problem, (ATS)  
79 690-694
- emotional problems in treatment of, (editorials)  
71 299-301
- endobronchial
  - in children, 74 (Supplement, August 246-255),  
77 39-61
  - occult, in surgical lung specimens, 77 931-939
- epidemic, 75 432-441
  - after antityphoid vaccine inoculation, 71  
465-472
- epidemiology, 67 123-131, 75 975-86
  - aspects, 68 1-8
- eradication, (editorials) 59 707-709
- evaluation of method of quantitative air-borne  
infection and its use in study of patho-  
genesis of, 61 765-797
- evolution, in long observed group, 75 885-896
- experimental
  - 4-acetylaminobenzal thiosemicarbazone in  
and dihydrostreptomycin, compared with  
PAS dihydrostreptomycin, 63 339-345
  - in guinea pigs, 62 144
  - adrenocortical hormones in, (Notes) 77 536-  
538
  - allergy in, 72 171-195
    - gross lesions, and culturable bacilli in mice,  
78 226-234
  - alteration of pulmonary arterial circulation  
in monkeys, 65 48-63
  - antagonism of isoniazid-streptomycin in  
mice infected with *M. tuberculosis*  
*H37Rv*, (Notes) 68 277-279
  - antituberculosis drug therapy in mice, 69  
104-110
  - arrested, isoniazid in, (Notes) 79 246-250
  - and BCG
    - effect on mice, 68 451-454
    - in guinea pigs
      - cortisone in, 69 511-519
      - vaccine and hyaluronidase in, 68 188-198
    - bovine
      - corticotropin and dihydrostreptomycin  
alone and combined, in rabbits, 67  
201-211
      - strains, 68 220-228
  - chemotherapy
    - effect on leukocytic sensitivity to tuber-  
culin, 77 815-822
    - with sulfones in the mouse, 63 556-578
  - in chicks, avian tuberculosis in, 60 366-376
  - choice of mouse strain, 60 109-120
  - choice and standardization of culture, 60  
90-108
  - chronic, 73 378-389
    - streptomycin in, 66 194-212
  - corticotropin-cortisone in, 68 31-41
    - in guinea pigs, 64 295-306
  - corticotropin and dihydrostreptomycin alone  
and combined, in rabbits, 67 201-211
  - cortisone in, 62 337-344, 65 64-74
    - corticotropin in, with and without anti-  
microbial therapy, 70 623-636
  - dihydrostreptomycin, in guinea pigs,  
(Notes) 67 101-102
  - effect on tuberculous lesions in guinea pigs,  
62 337
  - streptomycin, in albino rats, 65 596-602
  - treated, and alloxan-diabetic albino rats  
compared, 65 603-611
  - cycloserine in, (Notes) 72 117-118, 856-858,  
75 510-513
  - dihydrostreptomycin-PAS in, 62 149-155
  - dissemination of tubercle bacilli in guinea  
pigs, 61 399-406
  - drug screening, in guinea pigs, 68 48-64
  - effects
    - estrogen and chorionic gonadotropin in  
tuberculosis in rabbits, 59 168-185
    - estrogen and gonadotropin on progress of  
tuberculosis, 59 198-218
    - estrogen on tuberculin skin sensitivity and  
allergy of internal tissues, 59 186-197
    - tuberculin fractions on leukocytes from  
normal and tuberculous animals,  
65 250-271
  - embolic, pulmonary, in mice, 69 419-442
  - gauze masks, efficiency in protection of rab-  
bits, 59 1-9
  - genetic resistance in rabbits, 72 297-329
  - glycoprotein serum concentrations in guinea  
pigs, 68 594-604
  - guinea pig omentum as index of chemother-  
apy, 68 583-593
  - guinea pig resistance to tubercle bacilli with  
BCG, (Notes) 72 539-542
  - in guinea pigs vaccinated with BCG, 60 547-  
556
  - 5-heptyl-2-thiohydantoin, 78 74-82

*Tuberculosis, experimental, cont*

- heterocyclic acid hydrazides and derivatives
  - in, 67 366-375
- hog gastric mucin in, (Notes) 77 1005-1011
- hormone effect on virulent, attenuated, and avirulent mycobacteria in mice, 69 790-796
- hyaluronidase in, 63 108-115
- immunity in, 78 203-225
  - natural energy, artificial desensitization in, 78 235-250
- immunogenicity of BCG cultured in bile for guinea pigs, 59 102-105
- infection
  - air-borne, in rabbits, 73 315-329
  - in mice, 60 90-108, 109-120, 121-130, 72 330-339
- inhibited by isoniazid, 75 295-302
- irradiated antituberculosis vaccine and BCG
  - in guinea pigs, 67 341-353
- isolation of tubercle bacilli from feces and gastric contents of mice, 62 481
- isoniazid in, 73 1-18
  - in cats, 65 376-391
  - in combined chemotherapy of mice, 68 411-418
  - derivatives in, 67 354-365
  - in dogs, 65 376-391, 392-401
  - in guinea pigs, 65 365-375, 376-391, 68 75-81
    - early treatment with, 76 732-751
  - in mice, 65 357-364, 376-391, 392-401
  - in prevention, 74 917-939
  - prophylaxis in, (Notes) 77 999-1004
  - in rabbits, 65 365-375, 376-391
  - radioactive, action on, 67 490-496
  - in rats, 65 376-391, 392-401
  - streptomycin, in guinea pigs, 68 575-582
  - PAS-resistant, in guinea pigs, 66 477-485
- laboratory operation and design for, 68 212-219
- lethal allergic shock in, (correspondence) 75 343-348
- leukocyte lysis related to tuberculous serology in rabbits, 69 1002-1015
- liquefaction of tubercles, endocellular proteinases in tubercles developing in rabbit lungs, 63 694-705
- meningitis produced by lumbar intrathecal inoculation in guinea pigs, 66 722-731
- in mice
  - antituberculosis chemotherapeutic activity in, 64 541-550
  - lung density as measure of, 77 681-693
  - relation between size of infecting dose and survival time, 64 534-540
  - thiosemicarbazones in, (correspondence) 60 539
  - Triton A-20 alone and in combination with dihydrostreptomycin, 65 718-721
  - in monkeys, 72 204-209
  - isoniazid potentialities in, 74 (Supplement, August 138-153)
  - mycobactin in, 71 566-572
  - neomycin in, 62 345-352
    - in guinea pigs, 62 300-306, 345-352
  - nutrition and immunity in, 77 93-105
  - omentum vs pancreas in, (correspondence) 80 445-449
  - oxytetracycline in, 63 434-440
  - pancreas in, (Notes) 78 794-798
  - PAS, 78 753-759
    - streptomycin therapy in, 62 156-159
  - phagocytic stimulation of, in guinea pigs, (Notes) 73 442-443
  - phenazines in, 78 62-73
  - potassium iodide and streptomycin in guinea pigs, 64 102-112, 66 680-698
  - production of nontuberculous cavities in, by egg albumin, 75 99-104
  - pulmonary resection in rabbit, (Notes) 73 123-127
  - pyrazinamide
    - alone or in combination, 76 643-659
    - in guinea pigs, 65 519-522
    - isoniazid in, 69 319-333
    - in mice, 65 511-518
    - in vitro* and in guinea pigs, (Notes) 70 367-369
  - pyridine derivative in, (correspondence) 60 269-271
  - pyridine nucleotides in, before and during isoniazid therapy, 70 453-464
  - quartz dust inhalation effect on BCG, H37Ra, and *M. marinum* strains, 69 766-789
  - in the rabbit, 64 508-515
  - eye
    - adrenal hormones in, 66 175-187
    - as tissue to study, 64 197-206, 207-217
    - roentgenography as index of drug effect in, 68 65-74
    - tissue lipids in, 75 83-92
    - virulence of human and bovine tubercle bacilli in, 67 265-266
  - reproduction of sarcoidosis in guinea pigs, 60 236-248
  - screening of drugs in mice, 69 280-286
  - serum protein in
    - changes in, 77 120-133
    - in guinea pigs, 70 344-348
  - sex differences in mice related to immunity, 75 618-623
  - short-term therapy in, (Notes) 77 867-868
  - skin tuberculin reaction, 59 692-700
  - standardized test, for antituberculosis activity of compounds in, 60 121-130

*Tubercle as experimental, cont*

- streptomycin in, 59 661-673, 674-678, 60 62-77
- and PAS
  - in intracerebral infection of guinea pigs, 61 87-101
  - in mice, (correspondence) 60 808-810, 62 156
- viomycin, isoniazid, and streptomycylidene isonicotinyl hydrazine in mice, (Notes) 68 292-291
- streptovaricin in, 77 976-982
- sulfones in, 60 62-77
  - and streptomycin, in guinea pigs, 61 102-112
- taurine in, (Notes) 71 638-640
- test, with guinea pig, for tuberculostatic agents, 60 223-227
- thiocarbanidin in, 78 570-575
- thiosemicarbazone in, 62 114-118
- thioureas, substituted
  - in guinea pigs, 70 130-138
  - in mice, 70 121-129
- tissue fatty acids in resistance of rabbits to, 69 710-723
- triodothyronine and propyl thiouracil in, (Notes) 73 431-437
- tubercle bacillus wax in, 76 752-760
- tuberculin shock in mice, (Notes) 68 629-630
- vaccines and immunity in, 71 228-248
- viomycin in, 63 1-3, 4-6, 7-16, 17-24, 25-29, 30-35, 36-43, 44-48
  - acute and chronic toxicity, 63 44-48
  - in vitro* effects against tubercle bacilli resistant to certain drugs, 63 36-43
- virulence
  - in guinea pigs of isoniazid resistant cultures, (Notes) 68 290-291
  - of human tubercle bacilli for guinea pigs, 73 266-275
- extrapulmonary
  - pathogenesis of forms of, 62 (Supplement, July 48-67)
  - and pulmonary, PAS in, 61 613-620
  - suppurative, streptokinase-streptodornase in, 71 1-11
- fashionable in 1759, (correspondence) 80 110
- fatal, produced by BCG, (correspondence) 73 301-305
- Fibreglas®-plastic dust, influence on, 78 512-523
- fibrocaceous, isoniazid in, sputum culture and microscopy during treatment, 70 349-359
- future problem of, program for control of, 80 (Supplement, October 117-137)
- gastric, 61 116-130
- gel
  - diffusion precipitation techniques in, 77 450-461
  - diffusion tests in, 80 886-894
  - double diffusion test for, 80 153-166
- genital
  - female, (editorials) 75 501-505, (ATS) 524-527
  - transfer via semen, (case reports) 69 618-624
- genitourinary
  - streptomycin treatment of, 61 518-524
  - transmission of, (correspondence) 75 153-156
- in German population, U S Zone of Germany, 59 481-493
- global eradication of, 80 (Supplement, October 138-139)
- "good chronic case" of, (correspondence) 66 381
- in Hawaii, 68 839-862
- of the heart, 62 390-402
- hemagglutination
  - reaction
    - in children, 70 139-148
    - in diagnosis of, 64 71-76
  - test, 62 121-127, 223-226
    - complement-fixation modification (Mail-lard), (Notes) 66 621-622
    - hemolytic, 66 594-600
    - modification in, 65 194-200
- hematogenous, acute, in pregnancy in patient with tuberculous salpingitis, (case reports) 68 253-262
- hepatic
  - hypokalemia in, (case reports) 68 136-143
  - and sickle cell anemia, (case reports) 67 247-257
- histoplasmin sensitivity in, 78 667-681
- in Hong Kong, 76 215-224
- hospitals
  - and home in, including chemotherapy of, 80 (Supplement, October 23-45)
  - rehabilitation and occupational therapy in, (correspondence) 79 680
  - vocational rehabilitation, justification of, 80 59-64
- host resistance, relation of amino acids to, 66 378-380
- in humans
  - alpha-ethyl-thioisonicotinamide in, antituberculosis effectiveness of, 79 6-18
  - cycloserine in, (Notes) 74 121-127
  - kanamycin in, 79 72-77
  - natural history of, 79 19-30
- immunity, (editorials) 74 117-120
  - inhibition by chemoprophylaxis, 74 541-551
  - mechanism, relationship to pathologic changes, clinical symptoms, and therapeutic measures, (editorials) 68 933-937
  - and vaccines, 71 228-248

*Tuberculosis, cont*

- immunopathology of, 71 (Supplement, August 60-71)
- implications of changing morbidity and mortality rates from, 61 39-50
- in infancy and childhood, (case reports) 70 161-165, 73 422-433
- cortisone and corticotropin in, 74 (Supplement, August 209-216)
- incidence of, (Notes) 74 149-151, (correspondence) 808-809
- infection
  - air-borne, in rabbits, 73 315-329
  - evaluation of method and its use in pathogenesis of tuberculosis, 61 765-797
  - constitutional factors in resistance to, 59 168-185, 186-197, 198-218
  - difference in response of four strains of mice to immunization against, (Notes) 80 753-756
  - and illness, 71 885-888
  - among Indian tribes, 72 35-52
  - in infancy, (Notes) 74 149-151, (correspondence) 808-809
  - by injection of BCG, (correspondence) 72 869-870
  - murine, with *B. abortus* and *M. tuberculosis*, 73 251-265
  - mycobacterial, heterologous and homologous immunity in, 76 76-89
  - with streptomycin-resistant organisms, (case reports) 61 881-882
- influence on methylene blue reduction time of serum and heat coagulation value of plasma, (Notes) 70 907-909
- inoculation, after antityphoid vaccine, 71 465-472
- intestinal
  - chemotherapy as prophylaxis in, 64 430-441
  - PAS in, 61 621-642
  - streptomycin in, 60 576-588
- iodine in, (correspondence) 66 765-777
- isoniazid
  - cycloserine in, 75 553-575
  - pyrazinamide in, hepatotoxicity of, 80 371-387
  - serum concentrations and hemoglobin and methemoglobin values in, (Notes) 68 286-289
- among Jews, 67 85-93
- laboratory, routine, semi-synthetic autoclavable medium for, (Notes) 78 788-792
- lesions, relapse of, during and after chemotherapy, 80 (Supplement, October 47-71)
- lymphatic, 76 811-831
  - in children, enzymatic debridement of, 76 588-600
  - complications, 70 610-622
  - in neck, axilla, and groin, 73 229-238
  - treatment in accessible nodes, (editorial) 64 691-694
- mediastinal, 71 635-667
  - manifested by pericarditis, osteochondritis, and bronchoesophageal fistula, (case reports) 79 238-243
- in medical students at University of Maryland, 79 746-755
- meningeal
  - in adults, chemotherapy of, 68 912-925
  - in children, thiazolsulfone in, 61 159-170
  - isoniazid in, 66 391-415
  - in New York City, (Notes) 77 359-363
  - survival rate (1948-1955) in armed forces, 76 360-369
- mental aspects of, 62 532-538
- miliary, 61 138-144, 68 636-653, 77 605-622
  - in adults, chemotherapy of, 68 912-925
  - agranulocytosis in, 59 317-324
  - cardiac involvement in, (case reports) 68 771-774
  - in children
    - in New York City, (Notes) 77 359-363
    - streptomycin-thiazolsulfone in, 61 159-170
  - chronic, 62 549-554
  - icterus in, (case reports) 66 77-85
  - isoniazid in, 66 391-415
  - lupus erythematosus cells in, (case reports) 74 112-116
  - with meningitis and leukemia, (case reports) 70 509-517
  - and pregnancy, 62 209-212, (case reports) 68 253-262
  - survival rate (1948-1955) in armed forces, 76 360-369
  - treated with streptomycin, (case reports) 60 514-519
  - in vitro* susceptibility of tubercle bacilli in, 74 (Supplement, August 232-240)
- minimal, streptomycin in, 65 547-571
- morbidity
  - in mental patients and general population, 70 32-48
  - trend, 67 279-285
- mortality
  - in mental patients and general population, 70 32-48
  - in New York City, (Notes) 77 516-518
  - in Puerto Rico since 1950, (Notes) 70 1099-1101
  - among residents of large cities (1947-1949), 66 109-116
  - among World War II veterans (1953-1954), (Notes) 73 966
- movement, accomplishments and opportunities, 65 221-234

*Tuberculosis, cont*

- of myocardium, (case reports) 74 99-105
  - heart block change in, (case reports) 65 332-338
- natural history of, in humans, longitudinal observations imperative, (editorials) 80 100-107
- among the Navajo, 80 200-206
- in neonatal period, 77 418-422
- nephrectomy, partial, for, 66 744-749
- noninfectious, chemotherapy in, to prevent relapse, (correspondence) 80 108
- nonreactive, (case reports) 76 144-151, 79 362-370
- in nurses, pathogenesis of, 60 305-331
- and nutrition, 64 381-393
  - in adolescents, 74 (Supplement, August 173-183)
- ocular
  - adrenal hormones in, 66 175-187
  - in rabbits, 64 197-206, 207-217
    - corticotropin effect on, in decreasing dosages, (Notes) 69 1051-1053
    - streptomycin-isoniazid and somatotropic hormone effect on course of infection, 69 1016-1021
- omental, pathogenesis of, 73 362-370
- pain threshold in, 66 449-456
- paper electrophoresis in
  - as a progress index in, (Notes) 76 892-895
  - study of patients with, (Notes) 75 99-1002
- para-aminosalicylic acid for, 61 226-246
- preparations in, 78 899-905
- salt of isoniazid in, (Notes) 78 637-643
- sodium salt, administered subcutaneously, 64 557-563
- pathogenesis of, shown in omental spreads, 73 362-377
- patient(s)
  - attitude, evaluation of, 67 722-731
  - discharged, physical, psychologic, vocational, and socioeconomic status of, 69 153-163
  - hospitalized, adjustment on different wards, 79 273-283
  - leaving against medical advice, personality characteristics of, 67 432-439
  - nonhospitalized, 69 26-36, 75 41-52
  - rehabilitation of, (correspondence) 80 111-112
  - surgery refusal in, 77 311-322
- pericardial, 61 845-861
- peritoneal, 61 845-861
- pleural, 61 845-861
- and pneumococcosis, 3,3',5-triiodo-L-thyronine in survival time of mice with, 79 339-343
- precipitin test for carbohydrate antibodies in, (correspondence) 59 710-712
- prevalence, tuberculin conversion rates as indication of, 69 227-233
- primary
  - and antimicrobial therapy
    - in children, 69 682-689, 73 305
    - and prognosis of, (correspondence) 70 535-536
  - in children
    - bronchoscopy in, 74 (Supplement, August 267-278)
    - segmental atelectasis in, 79 597-605
    - segmental lesions in, 79 756-763
    - value of follow-up studies, 64 499-507
  - of faucial tonsil, (case reports) 69 612-617
  - systematic treatment of, 74 (Supplement, August 191-196)
  - tubercle bacilli in, late discharge of, 79 31-40
- among prisoners, San Joaquin County (California), 73 882-891
- probable, and steatorrhea, with hypogammaglobulinemia, (case reports) 74 773-782
- prophylaxis, in children, 74 (Supplement, August 75-89)
- protein serum concentrations in, electrophoretic studies of, 68 372-381
- psychologic aspects of, (editorial) 67 869-873
- in psychotic patients, 59 289-310, (editorials) 68 782-785
- collapse therapy in, 67 232-246
- in Puerto Rico, 67 132-153
- pulmonary
  - active, minimal, "modified" bed rest in, 61 809-825
  - with Addison's disease and histoplasmosis, (case reports) 72 675-684
  - adrenocortical function in, 64 630-644, 66 364-372
  - advanced
    - after-history of, 70 995-1008
    - outcome after 15 to 25 years, 72 487-501, 502-512
    - viomycin in, 70 812-840
  - aerial dissemination of, 76 931-941
  - after history of, method of evaluation, 69 37-49
  - ambulation and chemotherapy in, 70 1030-1041, (correspondence) 71 602-603
  - amithiozone in, 64 170-181, 65 692-703
  - angiography, 71 810-821
  - antimicrobial therapy *See* chemotherapy, below
  - aureomycin in, 59 624-631
  - bed rest and physical activity in recovery from, 75 359-409



*Tuberculosis, pulmonary, cont*

- bronchial disease in lungs resected for, 68 657-677
- bronchial preoperative biopsy in, 78 839-847
- and bronchogenic carcinoma, 61 369-386, 73 853-867
- bronchography, 64 394-407, 70 274-284
- preceding surgery, 77 561-592
- bronchspirometry
  - before and after resection and lobectomy, 75 710-723
  - of pulmonary function after decortication, 66 509-521
- C-reactive protein in, (Notes) 74 464-467
- chemotherapy of, 69 1-12
  - comparison of effect of four variables, 72 718-732
  - high doses of isoniazid with PAS and pyridoxine, (Notes) 78 773-784
  - isoniazid, streptomycin, and PAS compared as two-drug regimens, 72 756-784
  - lesions after prolonged use, 71 165-185
  - phenomenon of open-cavity healing, (editorials) 71 441-446
  - prolonged indefinitely, 70 219-227
- streptomycin
  - and isoniazid with PAS and pyridoxine, (Notes) 78 773-784
  - and PAS, three regimens compared, 72 733-755
  - and systemic blastomycosis, (case reports) 68 615-621
- chronic
  - effect of artificial pneumoperitoneum on ballistocardiogram, 66 52-57
  - fibrocaceous, relapse rates after, (Notes) 71 302-304
  - fibroid, potassium iodide and PAS in, 64 77-80
  - hepatic damage in, 72 71-90
  - massive dose isoniazid with pyridoxine in, (Notes) 78 474-477
  - treatment-failure, cycloserine and high-dose isoniazid in, (Notes) 80 269-273
- coexistent with coccidioidomycosis, 67 477-489
- coexistent with fungal disease, (case reports) 72 667-674
- comparison of isoniazid, streptomycin, and streptomycin-PAS in, (Notes) 66 632-635, (Notes) 67 108-113
- complicated with spontaneous pneumothorax, 74 351-357
- corticotropin, PAS, and streptomycin in, 66 542-547
- and cycloserine
  - psychologic effects of, (Notes) 73 438-441
  - pyrazinamide in, (Notes) 76 1097-1099, 78 927-931
  - viomycin in, (Notes) 79 90-93
- decortication of lung in, 59 30-38, 60 288-304
- development over prolonged period of time, 66 1-15
- diagnosis, tracheal lavage and culture in, 60 634-638
- and dihydrostreptomycin, 62 572-581
  - sulfate in, neurotoxicity of, 65 612-616
- disposition and follow-up, 60 487-500
- drug resistance in resections, 75 781-792
- drug-treated, cystic cavities and, 77 221-231
- effect of nontuberculous pulmonary inflammation on, 59 68-75
- emotional factors in, 62 428-433
- in employees of tuberculosis hospitals, 66 16-27
- empyema in, 59 601-618, 78 411-425
- S-ethyl-L-cysteine in, (Notes) 74 142-144
- exacerbation of, with special reference to allergy, (correspondence) 74 155-157
- extraperiosteal Lucite plombage in, 68 902-911
- and extrapulmonary PAS in, 61 613-620
- gas mixing in, 74 343-350
- in group continuously observed and periodically re-examined, 66 1-15
- healing
  - of open cavity in, 73 944-955
  - rate, with chemotherapy, 76 988-1001
- hematogenous, cardiopulmonary function in patients receiving streptomycin, 64 583-601
- hemorrhage in, 62 324-330
  - fatal, 60 589-603
  - pneumectomy for, 61 426-430
- hepatic derangement in, 76 410-425
- hiconstarch in, 73 219-228, 77 952-967
- histologic study of blood vessels in resected lung, 64 489-498
- in humans
  - isoniazid serum concentrations and therapeutic response in, correlation of, (correspondence) 80 108-110
  - thiocarbanilide SU 1906 in, (Notes) 74 468-470
- hydroxyethyl sulfone in, 68 103-118
- hypopotassemia and hyponatremia in, during treatment with streptomycin-PAS, 66 357-363
- immobilization of lungs in, 66 261-270, (correspondence) 778-780
- inactive, reactivation of, 73 31-39
- incidence and significance of thromboembolism in, 61 826-834
- indolent, diffuse, 71 503-518
- infectivity of, related to sputum status, 69 724-732

## Tuberculosis

influence of external factors on, 62 539-542  
 intermittent positive pressure breathing in,  
 72 479-481  
 international survey (Notes) 73 128-133  
 involving lower lobe artificial pneumothorax  
 in 59 50-52  
 isolated oil bronchography, 66 699-721  
 and isoniazid, 65 429-442, (correspondence)  
 71 314-317, (Notes) 73 117-122  
 adrenal cortical function during treatment,  
 70 541-551  
 alone in, (correspondence) 70 921-925,  
 71 903-916  
 ex lobe cavities during therapy, (Notes)  
 69 1054-1056  
 -cycle crime in, (Notes) 79 57-59  
 and electrophoretic serum proteins, 70 334-  
 343  
 high dose, (Notes) 77 539-542  
 long term 70 228-235  
 pathology of lesions, 71 189-192  
 peripheral neuropathy in, (case reports)  
 68 458-461  
 -streptomycin, (Notes) 80 424-425, 431-433  
 -treated, surgical pathology of, (Notes)  
 68 111-119  
 and liver, clinical, functional, and needle  
 biopsy study of, 63 202-209  
 lower lobe, 59 37-49, 60 1-14  
 lung function in, 79 474-483  
 lobular resection for, 79 465-473  
 lung immobilizer therapy in, (correspondence)  
 67 267  
 mass roentgenography in, 60 466-482  
 in medical and nursing students, 63 332-338  
 minimal, 76 64-75  
 after history of, 70 15-31  
 confined to apex of one lung, treatment of,  
 63 644-656  
 five year follow up, 73 818-830  
 in military personnel, 75 1-40  
 modified bed rest in, 67 101-120  
 rest and exercise in, 69 50-57  
 with and without chemotherapy, 73 818-830  
 moderately advanced, after history of,  
 71 519-528  
 mouse test for, (Notes) 77 1005-1011, 1012-  
 1016  
 mouth wash-membrane filter cultures in,  
 71 371-381  
 multiple drug therapy in, 76 540-558  
 nasal swab cultures in, (Notes) 80 909-910  
 new and untreated, isoniazid- and strepto-  
 mycin resistant tubercle bacilli in,  
 (Notes) 71 293-296  
 in New York State penal institutions, 61 51-56  
 neomycin aerosol in, (Notes) 78 135-137

noncavitary, isoniazid and isoniazid-PAS in  
 original chemotherapy of, 80 641-647  
 in noninfectious patient with cavity, resection  
 for, 74 169-177  
 open, transition to sarcoidosis, (case re-  
 ports) 78 769-772  
 oxytetracycline-streptomycin in, 66 534-541  
 PAS in, (Notes) 73 117-122  
 treatment, 61 597-610  
 para-isobutoxybenzaldehyde thiosemicarba-  
 zone in, failure of, (Notes) 68 791-  
 793, 794-795, 796-798, 799-802  
 pathology of, 61 543-555  
 lesions in, 71 (Supplement, March 1-244)  
 peptic ulceration following surgery, 74 358-  
 366  
 in persons observed from childhood, 75 885-  
 896  
 in persons over forty, 59 469-480  
 phrenic nerve interruption in, 60 168-182,  
 183-188  
 physical activity during convalescence,  
 energy cost of, 71 722-731  
 plasma viscosity and erythrocyte sedimenta-  
 tion determinations in, 69 595-598  
 pneumonectomy in, 77 73-82, 260-270, 78 822-  
 831  
 pneumoperitoneum in  
 effect of liver function, 65 589-595  
 effect on respiration, 70 672-688  
 with phrenic paralysis for, 61 323-334  
 with streptomycin and PAS in, 69 963-967  
 post primary, (correspondence) 73 598-600  
 frequency according to pulmonary arterial  
 pressure, 78 536-546  
 prediction of relapse, 73 472-484  
 and pregnancy, (case reports) 66 86-89  
 after pneumonectomy for, 78 563-569  
 preresection drug therapy in, 79 41-46  
 with primary pulmonary carcinoma, 79 134-  
 141  
 progression of, 66 666-679  
 protective antibody in, passive transfer of,  
 76 256-262  
 protein hydrolysate in, 59 511-518, 519-538  
 psychosocial factors in, 75 768-780  
 psychosomatic study of, 71 201-219  
 after pulmonary excision for nontuberculous  
 disease, 61 835-844  
 pyrazinamide, 65 523-546, (case reports)  
 69 443-450  
 alone and in combination with streptomy-  
 cin, PAS, or isoniazid, 60 413-422  
 -isoniazid, 69 319-350, (Notes) 70 743-747  
 low dosage, 74 400-409  
 or PAS, (Notes) 79 102-104  
 Rasmussen's aneurysm in, 60 589-603  
 of recent origin, isoniazid in, 71 841-859

*Tuberculosis, pulmonary, cont*

- recrudescence, early, in, 65 673-691
  - recurrent laryngeal nerve paralysis as complication of, (case reports) 65 93-99
  - reinfection and apical localization
    - blood layering in dog heart, 70 570-576
    - of experimental emboli, 70 557-569
    - stream flow theory, 70 547-556
  - relapse
    - factors in, 72 613-632
    - and mortality, 70 601-609
    - with and without chemotherapy, 79 612-621
  - relation of
    - to bronchogenic carcinoma, 64 620-629
    - to nutritional status, 62 58-66
  - resection, 59 10-29, 71 349-360, 73 79-98, 74 29-41
    - bilateral, 68 885-901, 74 367-375, 75 259-265
    - bronchial ulceration after, 69 84-91
    - of bronchus, 74 874-884
    - drainage following, (Notes) 69 636-637
    - in Hawaii, 80 6-11
    - of isoniazid-treated lesions, 70 102-108
    - of post-treatment residual lesions, 73 165-190
      - in resected specimens, 71 830-840
      - segmental, 69 554-565, 70 285-295
      - simultaneous, and thoracoplasty, 65 159-167
    - streptomycin-protected in, 67 22-28
  - residual volume, bilateral, determination of, 78 376-390
  - respiratory function impairment in, 71 333-348
  - re-treatment with viomycin, (Notes) 72 843-845
  - roentgenography
    - mass, 65 451-454
    - serial, interpretation of, 64 225-248
    - spread of, during sanatorium residence
      - before use of prolonged chemotherapy, 68 863-873
      - and surgical findings, comparison of, (Notes) 71 452-456
    - unreliability of diagnosis by, 69 566-584
  - serology of, 68 739-745
  - serum enzymes in, (Notes) 79 251-252
  - serum gamma globulins in, (correspondence) 61 893-894
  - serum protein fractions, electrophoretic and chemical, in, 67 299-321
  - simian, isoniazid in, 74 (Supplement, August 138-153)
  - streptomycin, (Notes) 73 117-122
    - dihydrostreptomycin in, comparison of, 68 229-237, 238-248
    - first clinical trial, (case reports) 71 752-754
    - five-year outcome, 71 193-200
    - intermittent regimens, analysis of patients treated with one or two grams every third day, 63 275-294
    - once weekly in, 69 980-990
    - with other forms of therapy for, (editorials) 60 264-268
    - PAS in, (Notes) 72 242-244
      - intermittent regimens, comparison with daily dosage schedules, 63 295-311
      - and pneumothorax in, 59 539-553
    - refractory, pneumonectomy and streptomycin for, (case reports) 66 605-614
  - streptomycyclidene isonicotinyl hydrazine sulfate, in, 70 701-713
  - streptovaricin alone in, (Notes) 80 426-430
  - surgery in, 73 690-703, 80 207-215, 80 (Supplement, October 95-115)
    - complicated by Horner's syndrome, 67 94-100
    - electrocardiogram in, 65 443-450
    - indications for, 73 191-218
    - management of, (Notes) 76 902-905
    - total statistics in, 68 874-884
  - suture ligation and partial thoracoplasty in, 70 61-70
  - testosterone in, 68 165-176
  - thiocarbanidin-isoniazid in, (Notes) 80 590-593
  - thoracoplasty in, 59 113-127, 60 273-287, 62 645-653
    - failure as indication for resection in, 62 434-438
    - primary, 78 832-838
    - in ten-year follow-up, 69 930-939
  - three-year follow-up study on 202 cases treated with streptomycin, 62 563-571
  - tracheal lavage and culture in diagnosis for, 60 634-638
  - tuberculin
    - hypersensitivity in, (Notes) 74 474
    - skin reaction in, 78 399-402
  - vascular changes in lungs in, 75 410-419
  - verazide in, 78 251-258
  - viomycin, 69 543-553
  - vocational rehabilitation in, (editorials) 78 647-650
  - widespread, in 19-day-old infant, Promizole®-streptomycin in, 61 747-750
- rates, among prisoners, 74 590-596
- reactors, finding of, 71 406-418
- rehabilitation in Philadelphia (Pennsylvania), 62 190-208
- reinfection, streptomycin-resistant tubercle bacilli inoculation in, 74 253-276
- relationship of immunity mechanism to pathologic changes, clinical symptoms,

*Tuberculosis, laboratory and*

- and therapeutic measures in, (editorials) 68 933-937
- renal
  - calcification in, (case reports) 71 137-140
  - chemotherapy of, urine cultures during, 70 149-151
  - experimental studies on pathogenesis and prognosis of, 61 504-517
  - roentgenographic classification of, 67 601-612
- research
  - cooperative, clinical, (editorials) 68 263
  - cost, in United States, 60 393-405, 527-531
- resistance, 77 136-149
  - concept of, 62 (Supplement, July 3-12)
  - in guinea pigs vaccinated with BCG, 60 547-556
  - humoral factors in, 76 90-102, 78 884-898
- respiratory function in *See also* Pulmonary function and Respiratory function and in other chronic lung diseases (Soviet translation), 79 112-151
- revisited, a schema for 78 333-345
- risk of developing among children of tuberculous parents, 70 1009-1019
- sanatorium(s)
  - histoplasmosis in, 73 609-619
  - place of laboratory in, (editorials), 73 291-293
- scientific appraisal of new drugs in, (editorials) 61 751-756
- among Selective Service registrants, 60 773-787, 80 795-805
- serologic test
  - new, 64 675-681
  - value of absorption in, (Notes) 66 762-764
- serology of, hemagglutinin adsorption in, 67 657-664
- of aerosol surfaces, 61 845-861
- and sickle cell anemia, 65 735-743
- skeletal
  - in children with primary and tertiary tuberculosis, 75 897-911
  - treatment of, 71 (Supplement, August 124-133)
- somatotrophic hormone in, (correspondence) 71 319-320
- in South America, (correspondence) 67 676-678
- of spleen, with polycythemia, (case reports) 60 660-669
- sterility, female, in, (editorials) 70 1096-1098
- of stomach, 61 116-130
- streptomycin, 77 413-417
  - research project, 59 140-167
- stress and adrenocortical function, relationship with, 69 351-369
- in students, (Notes) 76 308-314
- studies in Muscogee County (Georgia), 73 157-164

- surgery in
  - combined with pyrazinamide-rifamycin, 77 83-92
  - thoracic, major, full-term delivery following, 78 697-711
- survey detected, ultimate fate of, 68 9-23
- survival of patients, 66 651-665
- susceptibility
  - familial, BCG as index of, 69 383-395
  - of normal and immunized mice to, relationship of sex to, (Notes) 80 750-752
- in Taiwan (Formosa), 80 359-370
- teaching in medical schools, (editorials) 60 140-142, 63 365-371
- therapy, 71 (Supplement, August 188-190)
  - immunity in, 78 199-511
  - rapidly effective, implications of, (editorials) 61 892
  - for 30 years in a municipal sanatorium, (editorials) 70 518-520
- thoracoplasty, preresection and postresection, in, 79 204-211
- thyroid in native resistance to, 79 152-179, 180-203
- tissue culture studies in resistance in, 79 221-231
- today and tomorrow, 67 707-721
- tracheal, 60 604-620
  - streptomycin for, 60 32-38
- tracheobronchial, 60 604-620
  - streptomycin for, 60 32-38
- treatment, 70 930-948, 72 1-11
- tuberculin negative, 63 501-525, (correspondence) 64 468-469, 469-471
- tuberculin reactions during isoniazid treatment, 69 733-744
- undetected, in economic groups, 70 593-600
- unsolved problems in, 70 391-401
- urban reservoirs of (ATS), 79 687-689
- of urinary tract, uremia from, (case reports) 73 110-116
- vaccination against, 74 (Supplement, August 28-31)
  - with nonliving vaccines, 80 340-358, 495-509, 676-688
- views in perspective, 74 (Supplement, August 290-296)
- viomycin in, 69 520-542
- vitamin A in, 64 381-393
  - metabolism in, 72 218-227
- vocational rehabilitation in, (correspondence) 79 543
- and World Health Organization, (editorials) 64 218-222
- Tuberculostatic agents
  - guinea pig test for, 60 223-227
  - present in animal tissues, (Notes) 63 119
- Tuberculostatic factor in normal human urine, 73 967

- Tuberculostatic substance possessing lysozyme-like properties in serum, 64 669-674
- Tuberculous patient(s)  
   cardiac symptoms in, 62 (Supplement, July 98-103)  
   at home, 76 1049-1062  
   hospitalized, personality and behavior in, 76 232-246  
   and personnel pressure, (correspondence) 76 912-914  
   psychiatric evaluation of, (correspondence) 74 807  
   rating of, 70 483-489  
   rehabilitation of, in Philadelphia (Pennsylvania), 62 190-203
- Tularemia, lung abscess in, (case reports) 65 627-630
- Tumor(s)  
   adenoma  
     bronchial, 75 865-884  
     and supernumerary bronchus, (case reports) 75 326-330  
   adenomatosis, pulmonary, (case reports) 60 258-263  
     alveolar, (case reports) 60 788-793, 61 131-137  
   carcinoma  
     alveolar cell, 79 502-511  
     pulmonary, 62 594-609  
     bronchiolar, (case reports) 78 632-636  
       terminal, with inflammation and fibrosis, 76 559-567  
   bronchogenic  
     with carcinoma of larynx, (case reports) 74 438-440  
   as a differential diagnostic problem in pulmonary disease  
     I from major bronchi without secondary infection, 63 176-193  
     II *ibid*, with secondary infection, 63 255-274  
     III peripheral from minor bronchi and bronchioles, 63 399-416  
   and pneumonia in adults, 76 47-63  
   preclinical, 69 164-172  
   in relation to calcified nodules in lung, 66 151-160  
   and silicosis, (case reports) 76 1088-1093  
   and thrombocytopenic purpura, (case reports) 67 509-513  
   tuberculoma of lung simulating, 61 431-435  
   tuberculosis, bronchiectasis, and calcification as related to, 64 620-629  
   and tuberculosis, pulmonary, 61 369-386, 73 853-867  
   of larynx, with bronchogenic carcinoma, (case reports) 74 438-440  
   of lung, primary, with pulmonary tuberculosis, 79 134-141  
   chest lesions, asymptomatic and circumscribed, 62 512-517  
   "coin" lesions of lung, (Notes) 73 134-138  
   endothelioma of pleura, case reports with surgical extirpation, 63 150-175  
   hamartoma, endobronchial, (case reports) 80 65-70  
   hemangiopericytoma of lung, (case reports) 77 496-500  
   hemangio sarcomatosis, generalized, erroneously considered generalized tuberculosis, 61 257-262  
   hematoma, extrapleural, complicating extrapleural pneumothorax, streptokinase-streptodornase in, 63 547-555  
   leukemia  
     alveolar-capillary block due to, (case reports) 80 895-901  
     pulmonary involvement in, 80 833-844  
   lymphosarcoma, pulmonary, with alveolar-capillary block and coccidioidomycosis, (case reports) 78 468-473  
   malignancy, pulmonary, cytologic diagnosis of, 61 60-65  
   mediastinal, 60 419-438  
     cardiospasm simulating, (case reports) 63 597-602  
   mesothelioma, pleural, (case reports) 71 280-290  
     diffuse, malignant, (case reports) 78 268-273  
   neoplasms  
     and mediastinal cysts, in children, 74 940-953  
     pulmonary  
       and eosinophilia, (case reports) 75 644-647  
       mass surveys for, 62 501-511  
   neoplastic disease, meningeal, simulating tuberculous meningitis, (case reports) 69 1029-1036  
   neuroma, acoustic, tuberculoma of cerebello-pontine angle simulating, (case reports) 63 227-229  
   nodules, pulmonary, solitary, found in survey, 79 427-439  
   papilloma of bronchus, (case reports) 78 916-920  
   papillomatosis, bronchial and tracheal, (case reports) 71 429-436  
   pulmonary  
     diagnosis and treatment, 59 353-363  
     solitary, 63 252-254  
   reticulum cell sarcoma, cryptococcal and tuberculous meningitis in, (case reports) 78 760-768  
   thymoma  
     cystic, and tuberculoma, possible confusion between, (case reports) 70 155-160  
     malignant, with myasthenia gravis, (case reports) 72 381-385

## Tween®

- albumin liquid medium, in differentiation of tubercle bacilli, (Notes) 79 810-812
- inhibitory action on D-29 mycobacteriophage inhibited by serum albumin, (Notes) 80 443-444
- 80 and serum, effect on phage, 77 134-145

## U

## Ulcer(s)

- BCG-induced, healing effect of isoniazid on, 74 7-14

## peptic

- and emphysema, 80 (Supplement, July 155-156)
- after surgery for pulmonary tuberculosis, 74 358-366

Ulceration, bronchial, after pulmonary resection for tuberculosis, 69 84-91

Ultrafiltration apparatus, (Notes) 63 718-720

Ultrasonics, exposure to, in comminution of mycobacteria, (correspondence) 76 914-915

Ultraviolet, Hi Intensity, for sterilization, (Notes) 71 457-458

Umbradil, in bronchography, 68 760-770

United States, irregular discharge in, (correspondence) 69 847-850

University of Maryland, tuberculosis in medical students at, 79 746-755

Urease activity in mycobacteriaceae, (Notes) 65 779-782

Urecholine in gastric dilatation following phrenic interruption, 62 331-332

## Uremia

- with sarcoidosis, (case reports) 60 236-248
- from urinary tract tuberculosis, (case reports) 73 110-116

Urethane of beta-methylcholine *See* Urecholine

## Urine

## human

- normal, tuberculostatic factor in, (Notes) 73 967

spectrophotometric determination, of PAS, (Notes) 64 577-578

pancreatin-quaternary ammonium treatment of, 74 616-621

PAS in, 76 1071-1078

## tests

- for detection of isoniazid, (Notes) 80 904-908
- simple paper strip, for PAS, (Notes) 80 585-586
- tuberculo-inhibitory activity of role of ascorbic acid in, 69 406-418
- from tuberculous patients, for amino acid metabolism study, 76 867-870

U S S R, translation, of review

from Puzik and Uvarova, 79 497-501

from Stepanyan, 79 142-151

## V

## Vaccination

antituberculosis, with nonliving vaccines, (Notes) 77 719-724

## BCG

as index of familial susceptibility to tuberculosis, 69 383-395

in Panama, (Notes) 67 522-525

purified tuberculin fraction, from unheated cultures in testing, (Notes) 69 300-303

in sarcoidosis, 62 408-410

in silicosis, 62 455-474

in Sweden, (correspondence) 79 678-679

and vole, 74 (Supplement, August 43-50)

of mice, against *C. immitis*, 74 245-248

against tuberculosis, 74 (Supplement, August 28-31)

with nonliving vaccines, 80 340-348, 495-509, 676-688

## Vaccine(s)

antityphoid, cutaneous and lymphatic tuberculosis after, 71 465-472

assay, tuberculin reaction in, 66 351-356

BCG *See* BCG

from gamma-irradiated *M. tuberculosis* and *Br. suis*, (Notes) 79 374-377

in immunization against experimental tuberculosis, 71 228-248

irradiated, antituberculosis, (Notes) 75 987-991

and BCG in experimental tuberculosis in guinea pigs, 67 341-353

studies with, 62 418-427

nonliving, in antituberculosis vaccination, 77 719-724, 80 340-348, 495-509, 676-678

Vascular changes in lungs in pulmonary tuberculosis, 75 410-419

Vena caval obstruction due to histoplasmosis, (case reports) 77 848-857

Ventilagram, expiratory, 80 724-731

Ventilation *See also* Pulmonary function

in chronic pulmonary emphysema, 74 210-219, 220-228

and respiratory gas exchange, mechanical respirators in, 80 510-521

effect on antituberculosis activity of thioethyl compounds, 74 68-71

helium-dilution method in study of, 79 450-456

lobar, in man, 73 330-337

measurements

in coal miners, 59 270-288

by Ventube, 75 303-318

*Ventilation cont*

- mechanics, in emphysema, 80 (Supplement, July 118-120)
- numerical expression of functionally effective portion, 62 17-28
- Ventilatory capacity, tests
  - index of expiratory force in, 78 692-696
  - maximal midexpiratory flow, 72 783-800
- Ventilatory efficiency, nitrogen clearance in, 72 165-178
- Ventilatory function, tests
  - in sanatorium or clinic, 60 149-167
  - value of, in evaluating patients for thoracoplasty, 63 76-80
- Ventilatory obstruction, maximal expiratory flow test for, 78 180-190
- Venturi principle, in measuring ventilation, 75 303-318
- Verazide
  - pharmacology, 76 316-359
  - in pulmonary tuberculosis, 78 251-252
  - and related hydrazones, antituberculous activity of, 76 331-345
- Vessel(s)
  - in pulmonary emphysema, 80 (Supplement, July 67-91)
- Veterans Administration
  - Armed Forces, cooperative studies of tuberculosis
    - antimicrobial therapy in primary tuberculous pleurisy with effusion, 74 897-902
    - resection in (1952-1955), 73 960-963
    - survival among patients with military and meningeal tuberculosis (1948-1955), 76 360-369
  - Army and Navy, cooperative study
    - April 1, 1949, to January, 1951, 72 718-732
    - February 1, 1951, to January, 1952, 72 733-755
    - August, 1952, to September, 1954, 72 756-782
  - streptomycin regimens, study of, July 1946-April 1949, 60 715-754
- Viability test, for suspensions of tubercle bacilli, (Notes) 66 95-98
- Viomycin
  - activity
    - antimicrobial, 63 7-16
    - against mycobacteria, 63 1-3
    - against *M. tuberculosis* and other microorganisms *in vitro* and *in vivo*, 63 17-24
  - anaphylaxis, (case reports) 75 135-138
  - cycloserine, in pulmonary tuberculosis, (Notes) 79 90-93
  - effect
    - on plasma electrolytes, 68 541-547
    - on renal function, 68 541-547
    - on tubercle bacilli, phase contrast and electron-microscopic studies of, (Notes) 73 296-300

- in experimental tuberculosis, 63 1-48
- acute and chronic toxicity, 63 44-48
- effects, *in vitro*, against tubercle bacilli resistant to certain drugs, 63 36-41
- pyrazinamide, in surgical therapy of tuberculosis, 77 83-92
- streptomycin, isoniazid, and streptomycin-diene isonicotiny hydrazine in experimental mouse tuberculosis, (Notes) 68 292-294
- toxicity in humans, 63 49-61
- in tuberculosis, 69 520-542
  - pulmonary, 69 543-553
  - advanced, 70 812-840
  - re-treatment, (Notes) 72 843-845

## Viruses

- infections, of respiratory tract, 80 315-325
- influenza, Asian, in 1957, pathology of, 79 440-449

Vital capacities, total and timed, for bedside and office use, 80 724-731

## Vitamin A

- metabolism, in tuberculosis, 72 218-227, (correspondence) 73 603-604
- in tuberculosis, 64 381-393

Vitamin analogues, inhibition of growth of tubercle bacilli by, 62 (Supplement, July 34-47)

Vitamin E deficiency, isoniazid in, 80 223-231

Vocal cord paralysis, 73 52-60

Vole and BCG vaccinations, 74 (Supplement, August 43-50)

## W

Washington, D. C., roentgenographic survey in (1948), 66 548-566

Wax of tubercle bacillus, immunogenicity for mice, 80 216-222

Wegener's granuloma of the lung, 78 21-37 *See also* Pneumococcoses

Welders *See* Pneumococcoses

Will Ross Medal (1954), 72 566-568

Win 5211 *See* 5-Heptyl-2-thiohydantoin

World Health Organization, and tuberculosis, (editorials) 64 218-222

## X

X-ray *See* Roentgenography

X-ray therapy *See* Radiation therapy

## Y

Yeasts and pathogenic fungi, tuberculostatic properties of culture filtrates of, (Notes) 66 623-625

## Z

Zephiran® *See* Benzalkonium chloride

Zinc, traces of, in glycerol, (Notes) 74 145-146

Zone electrophoresis, in starch gels, (Notes) 78 932-933







VOLUME LIX to VOLUME LXXX

January 1949 — — December 1959



# CUMULATIVE INDEX

---

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# INDEX OF AUTHORS

## A

- AARON, THEODORE H , 59 701-706
- ABELES, HANS, 65 128-141, 67 45-58, 69 26-36, 1057-1058, 70 901-902, 1042-1053, 72 143-150, 74 293-294, 75 41-52, 78 725-731, 79 359-363
- ABELMANN, WALTER E , 67 755-778
- ABERNATHY, ROBERT S , 70 547-556, 557-569
- ABO, TAKASHI, 77 519-523
- ABRAHAMS, JEROME, 70 285-295
- ABRAMOWITZ, SOL, 65 465-476, 68 127-135, 76 320-321, 80 902-903
- ABRAMSON, SAMUEL, 59 1-9, 168-185, 186-197, 198-218, 61 765-797, 65 631-634, 783-785, 73 315-329
- ABSHER, W K , 59 643-649
- ACETO, JOSEPH N , 68 157-164, 799-802, 74 641-644
- ACHARYA, B K , 78 203-225, 80 871-875
- ACKERMAN, ALFRED J , 61 299-322, 63 176-193, 255-274, 399-416
- ACKERMAN, HELEN, 60 359-365
- ACREE, PAGE W , 70 61-70, 763-783
- ADAIR, CHARLES V , 64 207-217
- ADAIR, FOSTER, 66 378-380
- ADAMS, RALPH, 59 353-363
- ADCOCK, JOHN D , 61 705-718, 66 58-62, 69 543-553
- ADDINGTON, MILTON C , 70 476-482
- ADHIKARI, PRASANT K , 80 825-832
- ADIAO, AMPARO C , 79 31-40
- ADLER, DENIS C , 69 940-956
- AFFLECK, MARGARET N , 75 519-520, 78 226-234
- AFFRONTI, LEWIS F , 79 284-295
- AGAR, HILDA D , 67 217-231
- AGIUS, E , 72 53-63
- AGOSTINI, EARL E , 77 356-358
- AGRESS, HARRY, 69 824-828
- AHN, A K , 78 815-821
- AJELLO, LIBERO, 78 576-582
- AKAWIE, SHIRLEY, 60 439-447, 448-454
- ALBRECHT, F KENNETH, 60 532-535
- ALDRIDGE, CLIFTON, 80 267-268
- ALEXANDER, A F , 80 (Supplement, July 141-146)
- ALEXANDER, HATTIE, 74 (Supplement, August 232-240)
- ALEXANDER, JOHN, 61 57-59
- ALEXANDER, ROBERT S , 65 505-510
- ALLAMANIS, J , 73 964-965, 74 (Supplement, August 197-208)
- ALLEN, ALBERT R , 79 680, 80 446-447
- ALLEN, GEORGE S , 74 581-589
- ALLEN, HARRY S , 68 136-143
- ALLEN, ROYAL L , JR , 77 184-188
- ALLEN, SINCLAIR T , JR , 77 848-857
- ALLEY, FRANK H , 63 381-398
- ALLGOWER, MARTIN, 59 562-566
- ALLI, JOSEPH H , 80 914
- ALLING, DAVID W , 68 37-49, 70 15-31, 995-1008, 71 519-528
- ALLISON, MARVIN J , 59 168-185, 186-197, 198-218
- ALLISON, STANTON T , 62 563-571, 65 612-616, 72 552-554, 74 400-409, 79 102-104
- ALLMARK, M G , 68 199-207
- ALT, W J , 74 388-399
- ALTMAN, DAVID P , 80 876-885
- ALTMANN, VLADIMIR, 77 221-231
- ALVERSON, CLARA, 69 419-442
- ALWAY, ROBERT, 71 765-766
- AMANO, S , 71 465-472
- AMATUZIO, DONALD S , 66 228-232, 357-363
- AMBERSON, J BURNS, 61 518-524, 69 520-542
- AMERICAN TRUDEAU SOCIETY, 59 106-112, 140, 60 681-682, 61 145-157, 274-299, 436-440, 760-764, 62 451-454, 556-561, 63 230, 496-500, 617-624, 729, 64 125-126, 223, 323-326, 476, 579-582, 65 100-110, 219-220, 351-356, 494-504, 643-653, 786-791, 66 104-123, 251-260, 389, 503-508, 641-649, 781-782, 67 114-122, 268-271, 396-399, 550-552, 679-705, 68 150-155, 302-306, 477-503, 636-655, 808-838, 946-973, 69 131-152, 313-317, 477-478, 649-655, 854-858, 1068-1073, 70 184-189, 380-381, 540-546, 756-761, 930-953, 1105-1110, 71 148-161, 326-332, 464, 607, 771-773, 904-926, 72 137-141, 256, 408-418, 559-567, 699-711, 73 145-156, 310-313, 449-450, 607-608, 790-794, 970-975, 74 163-168, 307-308, 484, 647-653, 814-819, 980-984, 75 157-168, 352-357, 524-528, 697-698, 859-864, 1012-1018, 76 164-166, 326-329, 513-515, 708-713, 920-929, 1112-1117, 77 191-201, 371-373, 553-560, 728, 874-875, 1036, 78 145-150, 285-331, 490-497, 655-660, 814, 957-960, 79 108-118, 258-263, 387-398, 549, 684-697, 822-852, 80 115-123, 282, 452-455, 597, 764, 921-924
- AMES, WENDELL R , 68 9-23
- AMIDON, E L , 77 848-857
- AMILL, LUIS A , 60 514-519
- AMRHEIN, ILA J , 66 436-448
- ANASTASIA, K N , 70 139-148
- ANASTASIADIS, ANASTASIOS A , 76 388-397, 588-600
- ANDÉR, L , 76 983-987
- ANDERSON, AUGUSTUS E , 71 503-518
- ANDERSON, GAYLORD W , 67 123-131
- ANDERSON, HARRY S , 68 382-392
- ANDERSON, LEIGHTON L , 69 71-77, 72 653-658
- ANDERSON, LUCIA E , 63 7-16
- ANDERSON, ROBERT J , 70 593-600, 71 406-418
- ANDERSON, RUDOLPH J , 71 609-616

- ANDLEIGH, H S, 78 644-646  
 ANDREWS, NEIL C, 74 874-884, 77 62-72, 78 839-847  
 ANDRUS, PAUL M, 62 170-175  
 ANGEL, R W, 71 889-891  
 ANGELL, FRANKLIN L, 61 747-750  
 ANGEVINE, D MURRAY, 68 657-677  
 ANGHELI, B, 79 522-524  
 ANGRIST, ALFRED A, 73 110-116  
 ANGUS, DARREL C, 70 166-170  
 ANNO, HISATO, 71 333-348  
 ANTHONY, ELEANOR, 70 1030-1041  
 AOTAMA, K, 67 545-546  
 AQUINAS, MARY (SISTER), 76 215-224  
 ARANY, L S, 61 881-882, 74 807, 78 632  
 ARMADA, ORLANDO, 68 874-884  
 ARMSTRONG, A RILEY, 70 907-909, 75 338-339  
 ARMSTRONG, B W, 71 249-259  
 ARMSTRONG, FRANK L, 68 238-248, 71 193-200, 72 242-244, 73 776-778, 77 413-417  
 ARONSON, M H, 69 26-36, 1057-1058, 70 1042-1053, 75 41-52, 461-468  
 ARONSON, CHARLOTTE FERGUSON, 68 713-726  
 ARONSON, DAVID L, 79 83-86  
 ARONSON, JOSEPH D, 62 408-417, 63 121-139, 717, 68 695-712, 713-726, 70 71-90, 72 35-52, 245, 74 7-14, 810-811, 79 83-86, 731-737  
 ASSELINEAU, J, 67 853-858  
 ATTINGER, ERNST O, 74 210-219, 220-228, 77 1-9, 80 38-45, 46-52, 53-58  
 ATWELL, ROBERT J, 75 846-848, 76 877-879, 880-887, 78 127-130, 399-402, 927-931  
 AUCHINCLOSS, J HOWLAND, JR, 76 22-32, 77 863-866, 78 191-202  
 AUERBACH, OSCAR, 59 601-618, 60 604-620, 61 845-861, 62 324-330, 64 419-429, 67 173-200, 70 191-218, 527-530, 71 165-185, 72 386-389, 75 242-258, 76 988-1001, 80 207-215  
 AYVAZIAN, JOHN H, 76 1-21  
 AYVAZIAN, L FRED, 60 305-331
- B**  
 BABCOCK, CLAUDE E, 70 109-120  
 BABIONE, ROBERT W, 62 518-524  
 BACHMAN, HENRY, 79 87-89  
 BACKERMAN, TOBEY, 69 173-191  
 BACOS, JAMES M, 67 201-211  
 BADGER, THEODORE L, 60 305-331, 65 1-23, 67 568-597, 755-778, 779-797, 74 317-342, 75 648-649  
 BAGBY, B B, 66 436-448  
 BAI, ANGEL F, 69 554-565  
 BAISDEN, LOUIS A, 68 425-438, 439-443, 444-450  
 BALA, JOHN, 68 42-47, 71 860-866  
 BALDRIDGE, G DOUGLAS, 63 672-673, 674-678  
 BALDWIN, EDWARD R, Bibliography, 62 (Supplement, July 114-119)  
 BALDWIN, R W, 68 372-381  
 BALTER, ABRAHAM M, 67 232-246, 68 782-785  
 BAN, BINDRA, 72 71-90, 76 799-810  
 BANKIER, J D H, 68 400-410  
 BARACH, ALVAN L, 66 778-780  
 BARBER, LOUIS M, 68 926-932, 73 882-891  
 BARBIERI, M, 72 315-355  
 BARBOUR, BLANCHE H, 77 172-176  
 BARCLAY, RALPH K, 69 957-962  
 BARCLAY, WILLIAM R, 60 385-386, 67 490-496, 68 794-795, 70 784-792, 71 556-565, 72 236-241, 713-717, 78 760-768, 79 543-544  
 BARRIST, ELLIS M, 61 735-737  
 BARRY, VINCENT C, 71 785-798, 73 219-228, 74 798-801, 75 476-487, 77 952-967, 78 62-73  
 BARSHAI, B, 66 605-614  
 BARTMANN, K, 74 475-476, 77 999-1004, 79 97-101  
 BARTON, HARRY C, 71 30-48  
 BARTZ, QUENTIN R, 63 4-6  
 BASS, H E, 59 632-635, 60 520-523, 61 158, 62 219-222  
 BASTARRACHEA, FERNANDO, 77 473-481, 79 246-250  
 BATES, DAVID V, 80 (Supplement, July 172-178)  
 BATES, RICHARD C, 63 332-338  
 BATTAGLIA, BIAGIO, 66 594-600  
 BATTEN, JOHN, 72 851-855  
 BAUM, GEORGE L, 74 624-632  
 BAUM, GERALD L, 77 162-167  
 BAUM, LEWIS F, 59 68-75  
 BAUM, OTTO S, 59 68-75  
 BAUMGARTNER, LEONA, 79 687-689  
 BAYAN, A, 66 219-227  
 BEACHAM, EDMUND G, 66 213-218, 68 136-143  
 BEALL, GILDON N, 80 716-723  
 BEARDSLEY, FREDERICK A, 59 402-414  
 BEASLEY, CARROLL, 69 599-603  
 BEATTY, ARCH J, 62 434-438  
 BECK, CLAUDE S, 71 904-924  
 BECK, FREDERICK, 62 58-66, 66 44-51, 68 238-248, 72 151-157, 242-244, 79 134-141, 80 738-743  
 BECKER, BARNEY B, 67 22-28, 69 636-637  
 BECKER, HAROLD J, 70 806-811  
 BECKER, M L, 76 892-895  
 BECKLAK, MARGARET R, 76 398-409, 77 209-220, 400-412, 79 457-467  
 BEESON, PAUL B, 62 403-407  
 BEHNISCH, ROBERT, 61 1-7  
 BEKKER, J H, 74 633-637  
 BELL, J CARROLL, 69 71-77, 75 992-994, 995-998, 76 152-158, 683-691, 80 108-110  
 BELL, JOHN W, 73 123-127, 74 169-177, 75 538-552, 77 593-604, 78 848-861  
 BELLOW, MARJORIE, 66 666-679  
 BENNETT, RICHARD H, 62 128-143  
 BENNETT, WARREN A, 76 503-505  
 BENSON, ELLIS S, 59 415-428

- BRANSON, LOUIS, 69 595-598  
 BRANSON, R E, 72 201-209, 76 225-231  
 BRANSON, W M, 65 376-391  
 BRANTIA, FRANCIS J, 79 756-763  
 BRARD, LI ROY, 60 576-588  
 BRPCL, BERNARD A, 59 656-663  
 BRERFORD, O D, 77 325-328  
 BRUG, GEORGE S, 74 121-127  
 BRUGER, LISLIE R, 69 406-418  
 BURGH, N-P, 75 710-723, 76 983-987  
 BRUGMANN, MARTIN, 72 268-273  
 BRUGQUIST, SYLV, 61 112-117  
 BRUGY, MALCOLM E, 75 581-587  
 BURKE, RUDOLPH, 59 632-635, 61 111  
 BURIN, LOUIS, 70 577-592  
 BURNATT, PHILIP E, 74 954-957  
 BRUNSTEIN, I LEONARD, 77 162-167  
 BRUNSTEIN JACK, 60 539, 63 556-567, 65 357-361, 67 351-365, 366-375  
 BRUNSTEIN, SIDNEY, 62 101-108, 63 419-458, 66 36-43, 70 370-372, 73 266-275  
 BRUNSTEIN, THEODORF C, 62 651-666  
 BERRY, J W, 60 51-61  
 BERRY, JAMES L, 71 964-967  
 BERRY, JOHN W, 72 373-380  
 BIRTE, STEPHEN J, 74 471, 78 773-778, 779-784, 79 344-350  
 BERTEAUX, SOIANGE, 72 330-339  
 BERTHROG, MORGAN, 77 136-149, 79 221-231  
 BEUTNER, L H, 78 637-643  
 BEYER, ALFRED M, 72 381-385  
 BHARGAVA, R K, 76 410-425  
 BHATTACHARYA, B K, 60 62-77  
 BIEHL, J PARK, 68 296-297, 70 266-273, 430-441, 77 605-622  
 BIGGS, RAY H, 66 364-372  
 BINCKLEY, FREDERICK M, 60 788-793  
 BIONDO, THOMAS, 76 761-769  
 BIRATH, G, 66 134-150, 75 699-709, 710-723, 724-729, 76 983-987  
 BIRD, KENNETH T, 75 529-537, 77 669-674, 675-680  
 BIRKELAND, JORGEN M, 61 556-559, 64 332, 520-533, 74 229-238, 239-244  
 BIRKHAUG, KONRAD, 59 567-588, 60 547-556, 63 85-95, 613-614, 66 335-344, 68 96-102, 188-198, 69 300-303, 511-519, 70 873-880  
 BIRNBAUM, STANLEY J, 78 697-711  
 BIRSNER, J W, 70 109-120  
 BJÖRNESJÖ, K B, 73 967  
 BLACK, J M, 73 805-817  
 BLACK, J P MYLES, 69 396-405  
 BLACK, JOICE, 65 272-277, 67 657-664  
 BLACK, THOMAS C, 61 335-345, 826-834, 68 615-621  
 BLADES, BRIAN B, 60 683-698  
 BLAIR, EMIL, 74 343-350, 78 1-7  
 BLAKER, ROBERT G, 79 152-179, 180-203  
 BLALOCK, F A, 77 764-777  
 BLANKENBERG, HERMAN W, 79 357-361  
 BLATT, NORMAN H, 69 192-204  
 BLATSIK, C F, 79 773-779  
 BLACOWF, W, 71 838-839  
 BLITZ, OSCAR, 62 213-218  
 BLOCH, HUBERT, 59 562-566, 61 270-271, 67 629-613, 828-852, 853-858, 68 734-738, 71 112-125, 228-218, 75 488-491, 495-500, 80 911  
 BLOCH, ROBERT G, 59 551-561, 77 245-259  
 BLOCK, JEROME, 68 382-392  
 BLONQUIST, EDWARD T, 77 172-176  
 BLOOMER, WILLIAM E, 61 346-352  
 BLOUNT, S GILBERT, JR, 69 71-77, 80 (Supplement, July 128-130)  
 BLUMFATHAL, B J, 79 764-772  
 BOAK, RUTH A, 68 31-41, 70 344-348  
 BOBROWITZ, I D, 66 750-757  
 BOCKING, DOUGLAS, 69 1002-1015  
 BOGARDUS, GEORGE M, 71 280-290  
 BOGSA, EMIL, 59 707-709, 61 226-246, 62 160-169, 63 190-192, 64 192-196, 67 676-677, 68 31-41, 69 396-405, 70 344-348, 74 153-155, 76 435-450, 912-914, 1110-1111  
 BOGFR, WILLIAM P, 61 862-867, 62 610-617, 64 453-460  
 BOJALIL, L F, 77 473-481, 543-545, 79 246-250, 80 554-558  
 BOLLINGER, BETTY, 62 300-306  
 BOLTJES, BRN, 61 738-741  
 BOND, JAMES O, 80 188-199  
 BONDI, AMEDEO, JR, 63 325-331, 65 272-277, 67 657-664  
 BONDURANT, STUART, 70 547-556, 570-576  
 BOONE, IRENE U, 76 568-578  
 BORDEN, CRAIG W, 68 177-187  
 BOREN, H G, 74 178-187, 79 764-772  
 BORIE, JEANNE M, 77 511-515  
 BORNSTFEN, SIEGBERT, 61 353-354, 68 796-798  
 BOSMAN, A RAE, 76 398-409  
 BOSSE, LOUIS, 78 788-792  
 BOSWELL, HENRY, 66 364-372  
 BOSWORTH, EDWARD B, 69 37-49, 930-939, 70 15-31, 995-1008, 71 519-528  
 BOUCOT, KATHARINE R, 62 501-511, 65 (Supplement, January 1-50), 69 164-172  
 BOUGAS, JAMES A, 75 865-884  
 BOVORKITTI, SOMCHAI, 74 (Supplement, August 246-255), 77 39-61, 271-289  
 BOWEN, JOHN F, 80 426-430  
 BOWER, GEORGE C, 78 468-473, 80 (Supplement, July 207-208)  
 BOWERMAN, E P, 75 259-265  
 BOWMAN, B U, JR, 73 907-916, 80 232-239  
 BOYACK, GERALD A, 75 584-587  
 BOYAR-MANSTEIN, MARIAL L, 63 694-705  
 BOYD, LINN J, 75 553-575  
 BOYNTON, RUTH E, 73 620-636, 75 442-460  
 BOZALIS, GEORGE S, 59 289-310  
 BRADLEY, ELIZABETH M, 62 101-108



- BRAHAM, STANLEY, 61 518-524  
 BRANTIGAN, OTTO C, 59 210-258, 80 (Supplement, July 191-201)  
 BRASHER, CHARLES A, 73 609-619, 75 938-948  
 BRATTON, A C, JR, 63 7-16  
 BRAY, HARRY A, 69 631-635  
 BRICKLER, I ALFRED, 78 8-16  
 BRIS, ATLANTA G, 67 106-107  
 BRITTE, MELVIN J, 79 672  
 BRITTAUCHER, ROBERT B, 66 228-232, 357-363  
 BRETEL, J, 68 167-170, 75 650-655  
 BRIDGER, J, 69 26-36, 70 363-366, 1012-1053, 75 41-52, 78 725-734  
 BREWER, LYMAN A, III, 60 119-138, 69 554-565  
 BREWER, WILLIAM D, 60 155-165  
 BRIDGE, EZRA V, 64 682-685, 71 581-589, 78 647-649, 749-752  
 BRINKMAN, GLOFFREY L, 69 458-463, 963-967, 80 732-737  
 BRISCOL, W A, 80 (Supplement, July 136-137)  
 BRISSAUD, H E, 74 (Supplement, August 221-224), 80 326-339  
 BRISTOL, LEONARD J, 68 65-74  
 BRITT, CLARENCE I, 78 839-847  
 BROFMAN, BERNARD L, 71 904-924  
 BRONSON, S MARTIN, 76 173-191  
 BROOKE WILLIAMS, R D, 67 732-754  
 BROSBE, EDWIN A, 73 123-127, 266-275  
 BROTHERS, GEORGE E, 59 364-390  
 BROUET, G, 79 6-18  
 BROWN, CHARLES D, 76 426-434, 78 791-798  
 BROWN, HALLA, 74 783-792  
 BROWN, HENRY A, 63 427-433  
 BROWN, HORACE D, 70 806-811, 74 59-67, 78-83  
 BROWN, JOHN W, 62 543-548  
 BROWN, LEE B, 73 79-98  
 BROWN, W, 80 (Supplement, July 155-157)  
 BROWN, WALTER B, 68 286-289, 73 593-596  
 BROWNE, NOEL C, 77 952-967  
 BROWNING, ROBERT H, 75 846-848, 76 777-879, 880-887  
 BRUCE, ROBERT A, 59 364-390, 62 29-44  
 BRUECKNER, HAROLD H, 69 759-762  
 BRUHIN, H, 80 559-568  
 BRUKARDT, DIANE T, 77 387-399  
 BRUM, VICTOR C, 76 33-46  
 BRUMFIELD, DANIEL M, 62 (Supplement, July 98-103)  
 BRISON, VERNON, 62 286-299, 65 768-770, 68 280-283, 631-633, 69 267-279  
 BUCHBERG, ABRAHAM S, 59 624-631, 77 245-259  
 BUCHTEL, BUELL C, 76 291-297  
 BUCK, MARGARET, 65 759-760  
 BUCKINGHAM, WILLIAM W, 62 434-438  
 BUCKLES, MAURICE G, 64 394-407  
 BUDD, VERA, 64 81-86, 68 557-563, 71 860-866, 72 539-542, 76 272-278  
 BUECHNER, HOWARD A, 68 775-781, 71 503-518  
 BULHILLER, EDWIN A, 79 622-630, 631-640  
 BUENTF, LOUIS, 68 902-911  
 BULLEN, WAITER F, 62 512-517  
 BUGIE, ELIZABETH J, 60 366-376  
 BUIHTR, VICTOR B, 71 71-87, 73 917-929  
 BUIHTR, K G, 69 155-157  
 BUNGARNER, JOHN R, 71 137-139, 72 659-662  
 BUNGL, ROGER, 61 20-38  
 BUNA, PAUL A, 61 263-268, 64 197-206, 207-217, 66 175-187, 67 652-656, 69 1016-1021, 1051-1053, 71 128-141, 76 703-705, 79 72-77  
 BURDON, KENNETH L, 64 170-181  
 BURGER, FREDERICK J, 65 519-522, 635-636  
 BURKE, HUGH E, 62 48-67, 79 52-65  
 BURKE, JOHN C, 65 392-401, 67 644-651  
 BURKE, RICHARD M, 75 921-937  
 BURNEII, JAMES M, 64 71-76  
 BURNETT, C A, 74 856-873  
 BURRII, ROBERT G, 74 229-238, 239-244, 78 259-267  
 BURROWS, BENJAMIN, 78 760-768, 79 543-544  
 BUSFMAN, UTE, 73 547-562  
 BUSH, D, 62 638-644  
 BUSHBY, S R M, 72 123-125  
 BUTLER, KATHARINE, 74 136-141
- C**  
 CABELLI, VICTOR J, 69 604-611, 76 697-702  
 CACCESE, ANTHONY, 66 52-57  
 CACCIA, P A, 75 105-110, 76 1071-1078  
 CADDE, A V, 62 645-653  
 CADE, ROBERT, 71 693-703  
 CALDEN, GEORGE, 67 722-731, 68 523-534, 70 483-489, 72 633-646, 73 338-350, 74 964-967, 77 311-322  
 CALDWELL, DAVID M, 77 644-661  
 CALI, ARTHUR A, 68 382-392, 69 334-350, 70 304-311  
 CALLANAN, J G, 74 358-366  
 CALWELL, H G, 73 301-305  
 CAMERON, GEORGE F, 64 564-571  
 CAMERON, HAMILTON, 70 533-537  
 CAMERON, VIRGINIA, 60 393-405  
 CANIEN, MERRILL N, 60 439-447, 448-454  
 CAMPAGNA, MAURICE, 69 334-350  
 CAMPBELL, GUI D, 66 364-372  
 CANADA, ROBERT O, 62 518-524, 563-571  
 CANETTI, GEORGES, 74 (Supplement, August 13-21), 75 650-655, 79 684-686  
 CAPLE, L H, 68 622-624  
 CARABASI, ROBERT J, 78 610-622, 79 543  
 CARABASSO, B, 71 867-876  
 CARABELLI, A ALBERT, 77 22-31  
 CARMICHAEL, ELIZABETH, 68 199-207  
 CARNEIRO, JOSÉ FERNANDO, 79 544-545  
 CARPENTER, CHARLES M, 60 359-365, 68 31-41, 70 344-348, 74 152, 79 374-377

- CARP, DAVID I, 63 427-433, 65 159-167, 69 78-83, 70 899-900, 71 971-977, 76 503-505, 78 617-619, 79 752-753, 753-759
- CARRITERO, ROSARIO, 71 (Supplement, August 216-235), 77 39-61
- CARROLL, D G, 71 219-259
- CARROLL, DOUGLAS, 63 231-251, 64 583-601
- CARROLL, I D, 71 302-301
- CARTAGENA, BO, 61 613-620, 67 258-260
- CARTER, MAX G, 69 1012-1011
- CARTON, ROBERT W, 76 167-172
- CARVAJAL, EUGENIA J, 76 1091-1096
- CARVAJAL, GUILLERMO, 76 1091-1096
- CASTILLO, HERMINIO DEL, 73 61-71
- CATTANEO, C, 75 793-806
- CAWTHON, WILLIAM U, 65 429-442, 66 391-415, 68 791-793
- CEDEQUIST, DIANA C, 60 455-465
- CELIS, ALJANDRO, 71 810-821
- CERNÓN, S J, 80 554-558
- CERRIOTTI, GIOVANNI, 69 101-110
- CHADWICK, R M, 72 356-366
- CHAIKOF, LEO, 80 732-737
- CHAMBERLAIN, W EDWARD, 69 566-581
- CHAMBERS, JOHN S, 76 852-861
- CHAMBERS, JOHN S, JR, 63 625-643
- CHANDRASEKHAR, S, 77 1030-1032
- CHANG, Y T, 63 100-107, 68 119-126, 79 673-676, 805-809
- CHAPMAN, GEORGE, 74 783-792
- CHAPMAN, JESSIE P, 71 137-139
- CHAPMAN, JOHN S, 71 459-461, 73 422-433
- CHAPMAN, PAUL T, 66 151-160
- CHARF, SOL, 73 438-441
- CHARAFF, JESSE, 61 577-578
- CHARR, ROBERT, 67 376-384, 71 877-884
- CHARTER, WILBUR V, 62 563-571
- CHAVES, AARON D, 59 169-180, 63 194-201, 65 128-141, 67 45-58, 598-603, 69 26-36, 70 363-366, 901-902, 1042-1053, 72 113-150, 74 293-296, 75 41-52, 76 732-751, 77 359-363, 516-518, 725-734, 80 535-586
- CHEN, GRAHAM, 59 692-700
- CHEVALLIER, J, 79 6-18
- CHIEF, JAMES T T, 69 818-823
- CHILDRESS, WILLIAM G, 62 114-118, 63 339-345, 65 692-708, 66 621-622
- CH'IU, PHILIP T Y, 60 483-486
- CHOPRA, I C, 70 328-333
- CHOREMIS, C B, 70 139-148, 72 527-536, 859-862, 73 964-965, 74 (Supplement, August 197-208), 76 263-271, 79 522-524
- CHOUKROUN, NINE, 59 710-712
- CHOY, SUN HAK, 73 99-109
- CHRISTIAN, EDWARD R, 67 247-257, 70 1083-1091
- CHRISTIE, FREDERICK J, 63 312-324
- CICERO, RAUL, 71 810-821, 73 61-71
- CINCOTTI, J J, 75 730-744
- CITRON, K M, 80 167-180
- CLAGETT, THERON O, 61 193-200, 65 159-167, 71 581-589
- CLAPS, FRANCIS X, 76 862-866
- CLARK, CHARLES M, 66 391-415
- CLARK, MARY E, 68 786-787, 80 741-746
- CLARK, BARBARA L, 69 92-103, 991-1001
- CLARK, EDMUND R, JR, 69 351-369, 73 795-804
- CLARK, ROBERT W, 71 596-599, 72 694
- CLAUDON, DANN B, 71 144-145
- CLAUSS, ROY H, 74 351-357
- CLAYTON, Y M, 80 167-180
- CLEMONS, HELEN, 62 618-631, 67 732-751
- CLERF, L H, 61 60-65
- CLINE, F, JR, 59 643-649
- COATES, E OSBORNE, 65 751-758, 69 458-463
- CORURN, FRANK E, 71 299-301
- COCCHI, CESARE, 71 (Supplement, August 209-216)
- COHEN, AARON A, 79 253-255
- COHEN, ARCHIBALD C, 62 539-542
- COHEN, DAVID H, 61 582-585
- COHEN, GOODMAN, 71 219-259
- COHEN, JACK D, 65 1-23
- COHEN, ROBERT V, 71 220-227
- COHEN, S S, 59 113-127
- COHEN, SAMUEL, 59 519-538, 62 360-373, 68 165-176
- COHEN, SUMNER S, 68 229-237, 70 739-742, 78 106-110, 899-905
- COHN, J E, 71 219-259
- COHN, JEROME, 78 682-691
- COHN, M L, 60 269-271, 63 108-115, 70 465-475, 641-661, 852-872, 1030-1041, 72 693, 75 656-658
- COLE, CLARENCE R, 63 538-546
- COLE, FRANCIS H, 71 295-298, 75 259-269
- COLF, LEON R, 80 398-403
- COLE, MITTON B, 80 915-918
- COLE, ROGER M, 62 403-407
- COLEMAN, C M, 74 42-49
- COLEMAN, CHARLES M, 69 1062
- COLLIN, E, 79 484-491
- COLLINS, D M, 70 274-284
- COLLINS, MARTHA D, 61 257-262
- COLN, ANN C, 63 372-380
- COLWOLD, HENRY P, 69 618-624
- COLWELL, CHARLOTTE A, 63 679-693, 71 272-279, 73 892-906, 75 678-683
- COMER, J V, 66 605-614, 70 191-218
- COMSTOCK, GEORGE W, 73 157-164, 77 877-907, 79 542
- CONALTY, MICHAEL L, 71 785-798, 799-809, 73 219-228, 75 476-487, 77 952-967, 78 62-73
- CONANT, JAMES S, 71 349-360
- CONANT, N F, 61 690-704, 70 498-503
- CONE, ROSS B, 67 509-513
- CONGE, G, 79 484-491
- CONKLIN, WILLIAM S, 68 885-901

- CONNORS, CONSTANCE J , 68 470-471, 69 128  
 CONWAY, JOHN D , 66 601-604  
 CONZELMAN, GAILORD M , JR , 74 739-746, 802-806  
 COOK, LEIGH, JR , 65 744-753  
 COOKE, GEORGE M , 71 371-381  
 COOLEY, DENTON A , 68 727-733  
 COOLEY, JAMES ALLEN, 59 650-655  
 COOPER, DAVID A , 65 (Supplement, January 1-50), 75 122-134  
 COOPER, PHILIP, 74 729-738  
 COPE, J H , 61 443-464  
 COPE, JEROME A , 74 92-98  
 CORAY, STEVEN, 80 264-266  
 CORCORAN, THOMAS E , 80 914  
 CORPE, RAYMOND F , 73 681-689, 74 92-98, 75 199-222, 223-241, 77 73-82, 764-777, 80 388-397  
 CORPER, H J , 60 269-271, 63 108-115, 65 722-734  
 COSTER, J F , 74 958-960  
 COSTIGAN, WILLIAM J , 68 65-74  
 COTTON, BERT H , 70 109-120  
 COUNIHAN, HENRY E , 73 219-228  
 COURNAND, ANDRE, 63 231-251, 64 583-601  
 COWAN, DONALD, 73 620-636, 75 442-460  
 CRAGE, WILLIAM D , 59 78-85  
 CRANDALL, ARCHIE, 74 457-461  
 CRANDALL, WILLIAM D , 59 325-335  
 CREGER, WILLIAM P , 60 343-353  
 CREITZ, JOSEPH, 71 126-130  
 CRELLIN, J ANTRIM, 69 657-672  
 CRENSHAW, GERALD L , 71 30-48  
 CRIEP, LEO H , 59 701-706, 67 535-537  
 CRISALLI, JOSEPH P , 79 531-532  
 CROCE, PIETRO, 73 785-786  
 CROFTON, JOHN, 77 869-871  
 CROMBIE, D W , 62 170-175  
 CROSS, D F , 72 228-230  
 CROW, HORACE E , 75 199-222  
 CROW, JOHN B , 67 859-868  
 CROWLE, ALFRED J , 77 290-300, 681-693, 80 (Supplement, July 153-154)  
 CRUMB, CRETYL, 65 201-205  
 CUGELL, DAVID W , 67 568-597, 74 317-342  
 CUIZON, ROD, 77 858-862  
 CULLEN, JAMES H , 72 231-235, 74 289-292, 76 33-46  
 CUMMEROW, ELIZABETH H , 66 335-344  
 CUMMINGS, MARTIN, 59 599, 60 228-235, 621-627, 628-633, 62 484-490, 632-637, 63 459-469, 65 596-602, 603-611, 66 345-350, 378-380, 70 637-640, 72 117-118, 685-686, 856-858, 73 246-250  
 CUMMINS, CHRISTOPHER, 74 188-195  
 CURRERT, ANTHONY R , 59 10-29, 74 29-41  
 CURRY, FRANCIS J , 73 501-518, 77 749-763  
 CURRY, JOSEPH L , 69 657-672  
 CURTIS, GEORGE M , 66 699-721  
 CURTIS, JOHN K , 72 569-576, 75 745-755  
 CUSHING, IVAN E , 79 315-322  
 CUSTER, EDWARD W , 79 378-381  
 CUTHBERT, JAMES, 61 662-677  
 CUTLER, J W , 71 600-603  
 CUYKENDALL, JAMES H , 72 373-380  
 CYSNER, ERNA, 65 779-782  
 CZAJA, Z GEORGE, 75 295-302
- ## D
- DAIL, M C , 69 464-468  
 DAILEY, JAMES E , 78 478-484  
 DALY, JOHN F , 76 588-600  
 DAMROSCH, DOUGLAS S , 74 (Supplement, August 232)  
 DANELATOU, C , 72 859-862  
 DANGLER, GERTRUDE, 70 349-359, 72 143-150, 74 293-296  
 DANIELS, GEORGE E , 62 532-538  
 DANIELS, J , 71 88-96, 97-111  
 DANIELS, MARC, 61 751-756  
 DARRICARRERE, RAFAEL, 68 96-102  
 DARZINS, E , 80 866-870  
 DASCOMB, HARRY E , 77 511-515  
 DASHER, WILLIAM A , 69 396-405  
 DAVEY, WINTHROP N , 61 705-718, 63 332-338, 66 58-62, 69 543-553, 70 623-636  
 DAVIDOFF, EUGENE, 62 532-538  
 DAVIDSON, HORACE B , 64 394-407  
 DAVIDSON, J , 74 485-510  
 DAVIES, PAMELA A , 77 271-289  
 DAVIES, ROBERTS, 75 768-780, 80 188-199  
 DAVIN, JULIA R , 61 643-647  
 DAVIS, BERNARD B , 65 631-634  
 DAVIS, EDGAR W , 74 106-111  
 DAVIS, J DWIGHT, 60 288-304, 62 525-531  
 DAVIS, MARTIN W , 52 594-609  
 DAVIS, REYNOLDS, 77 350-355  
 DAVIS, W E , JR , 72 345-355  
 DAI, GEORGE H , 68 634-635, 69 847-851, 73 597  
 DAYTON, ROY, 62 (Supplement, July 104-113)  
 DEAKINS, DUANE D , 68 926-932, 73 882-891  
 DE ALEMQUER, MARIO, 78 462-467  
 DEBAKEY, MICHAEL E , 68 727-733  
 DEBRE, ROBERT, 65 168-180, 72 869-870, 74 (Supplement, August 191-196, 221-224), 80 326-339  
 DECAMP, PAUL T , 70 61-70, 77 496-500  
 DECKER, ALFRED M , JR , 75 538-552  
 DECKER, JOHN P , 75 122-134  
 DEEB, EDWARD N , 72 543-547  
 DE FIGUEIREDO, FLAVIO POPPE, 76 871-876  
 DEIBERT, KIRK R , 75 139-144  
 DEICHES, HELEN, 68 631-633  
 DEISS, WILLIAM P , 62 543-548  
 DE J MACIAS, JOSÉ, 79 265-272  
 DE LA HUEGA, J , 77 120-133  
 DEL CASTILLO, HERMILO, 73 61-71  
 DEMETRIADES, ANDREAS D , 75 326-330  
 DEMONTE, A J H , 70 328-333

- DEMPSEY, MARY, 66 109-116, 68 177-187, 70 296-303  
 DENARO, SALVATORE A, 74 462-463  
 DENICOLA, RALPH, 62 128-143  
 DENNENY, JOAN M, 71 785-798, 75 476-487  
 DENNERLINE, RICHARD L, 76 752-760  
 DENST, JOHN, 64 489-498, 68 144-149, 70 1030-1041, 71 441-446, 73 944-955  
 DE PAOLA, DOMINGOS, 71 186-192, 76 871-876, 78 140-144  
 DE PINZON, TERESINA P, 67 522-525  
 DERBES, VINCENT J, 74 464-467, 79 251-252, 531-532  
 DES AUTELS, EUGENE J, 68 912-925  
 DESBORDES, JEAN, 66 382-383  
 D'ESOP, NICHOLAS D, 62 563-571  
 DES PREZ, ROGER, 75 659-666, 77 539-542, 80 431-433  
 DESSAU, FREDERICK I, 60 223-227, 65 519-522, 523-546, 635-636  
 DEUSCHLE, KURT, 69 319-333, 70 228-265, 743-747, 71 316-317, 72 851-855, 75 659-666, 76 1100-1105, 1106-1109, 77 539-542, 80 200-206, 415-423, 431-443, 904-908  
 DE VESTY, GERALDINE, 77 1005-1011  
 DEVINE, KENNETH D, 73 52-60  
 DEWING, STEPHEN B, 60 25-31  
 DEWITT, C W, 64 322  
 DEWLETT, HAL J, 78 773-778, 779-784, 79 344-350  
 DEYKE, VERN F, 63 275-294  
 DHOPESHVAREAR, G A, 78 117-120  
 DIAZ, RAPHAEL M, 77 221-231  
 DICARA, LEO V, 71 755-761  
 DICKIE, HELEN A, 59 10-29, 70 102-108, 72 690-692, 74 29-41  
 DIDCOCK, K A, 74 1-6  
 DIEFENBACH, WILLIAM C L, 62 390-402  
 DIENA, B B, 78 785-787, 79 816-817  
 DI FONZO, MARIA, 66 240-243  
 DILLON, ANN, 65 111-127, 70 1009-1019  
 DILLON, EDWARD S, 65 (Supplement, January 1-50)  
 DILLON, ROBERT F, 71 529-543  
 DILLON, ROBERT J, 73 165-190  
 DIXON, KENDAL C, 77 106-119  
 DIXSON, SHIRLEY, 79 492-496  
 DOANE, EDWIN A, 64 192-196  
 DOCKSEY, JOHN W, 71 573-583  
 DOERNER, ALEXANDER A, 64 564-571  
 DOLL, JAMES P, 80 262-263  
 DOLLEY, FRANK S, 60 419-438  
 DOMAGK, GERHARD, 61 8-19  
 DOMM, SHELDON E, 74 188-195  
 DOMON, CHARLES M, 60 564-575, 68 103-118  
 DONIKIAN, MARY A, 67 808-827, 69 173-191, 72 846-850  
 DONNERBERG, ROY L, 75 846-848, 76 877-879, 880-887  
 DONOHUE, ROBERT F, 80 590-593  
 DONOSO, H, 71 249-259  
 DONOVICK, RICHARD, 60 90-108, 109-120, 121-130, 140-142, 539, 63 556-567, 65 761-764, 66 219-227, 67 354-365, 366-375, 68 284-285  
 DOONEIEF, A S, 59 624-631, 60 557-563, 70 178, 219-227, 72 252  
 DOPPELT, HARRY B, 60 189-205  
 DOTTER, CHARLES T, 62 353-359  
 DOUB, LEONARD, 61 407-421, 77 301-310  
 DOUGLAS, R GORDON, 70 49-60, 78 697-711  
 DOUGLASS, BRUCE E, 63 427-433, 74 954-957  
 DOUGLASS, RICHMOND, 60 524-526, 69 930-939  
 DOUTHIT, VERA B, 79 543  
 DOWLING, HARRY F, 69 192-204  
 DOY, C H, 79 492-496  
 DOYLE, W, 78 637-643  
 DOZIER, SLATER M, 75 949-953, 954-957  
 DRAKE, CLIFFORD L, 79 374-377  
 DRASH, E CATO, 73 79-98  
 DREA, W F, 74 145-146  
 DREISHPOON, IRVING H, 70 49-60  
 DRESSLER, SIDNEY H, 64 489-498, 70 504-508, 1030-1041, 1102-1103, 71 390-405, 441-446, 73 944-955, 74 (Supplement, August 188-190), 80 111-112  
 DROBECK, BERYL, 64 197-206, 207-217, 66 175-187  
 DROLET, GODIAS, J, 61 39-50, 72 419-452  
 DROSOS, CH, 76 263-271  
 DRUMMOND, ELEANOR E, 76 579-587  
 DRUMMOND, MARGARET, 59 599  
 DRUSCH, HELENE E, 68 31-41  
 DUBIN, ALVIN, 77 120-133  
 DUBOCZKY, BELA O, 70 1092-1095  
 DUBOS, RENE J, 60 384, 385, 670-674, 63 119, 65 637-640, 67 874-877, 68 1-8, 70 391-401, 73 781-784, 74 117-120, (Supplement, August 1-6), 541-551, 655-666, 667-682, 683-698, 699-717, 79 80-82, 484-491  
 DUBOSE, HOWARD M, 66 345-350, 76 47-63  
 DUERR, EDITH L, 75 506-509  
 DUFFY, ROBERT W, 73 831-852  
 DUFOUR, EMMA H, 62 77-86, 69 585-594, 71 704-721  
 DUKE, C JAMES, 80 590-593  
 DUMBOVICH, BORIS, 77 1017-1018  
 DUNBAR, FRANK P, 77 350-355, 79 669-671, 80 188-199  
 DUNHAM, WOLCOTT B, 72 119-122  
 DUNN, KATHARINE REMINGTON, 60 439-447, 448-454  
 DUNN, MAX S, 60 439-447, 448-454, 75 688-691  
 DUNNER, EDWARD, 62 563-571  
 DU FREEZ, L, 77 400-412  
 DUROST, H B, 71 201-219  
 DURR, FREDERICK E, 80 876-885  
 DURRANCE, JOHN R, 78 604-609  
 DUSHANE, JAMES W, 74 940-953

DUTTON, ROBERT, 78 191-202  
 DWORK, RALPH E, 60 45-50, 79 427-439  
 DWORSKI, MORRIS, 62 455-474, 69 766-789, 841-842  
 DYE, WILLIAM E, 61 719-724, 63 275-294, 295-311, 66 534-541, 67 106-107

## E

EARLY, LAWRENCE J A, 74 289-292  
 EASTMAN, GERARD, 78 191-202  
 EATON, J LLOYD, 74 476-478  
 EBERT, RICHARD V, 68 177-187, 80 (Supplement, July 45-49, 169-171, 209-212)  
 EBERT, ROBERT H, 59 554-561, 65 64-74, 67 490-496, 68 794-795, 70 784-792, 71 556-565, 75 71-72  
 EDDIE, B, 74 566-571  
 EDGAR, JANICE, 76 331-345  
 EDGE, J R, 74 747-755  
 EDLING, J H, 74 128-135  
 EDWARD, DEIRDRE WALDRON 77 952-967, 78 131-134  
 EDWARDS, HERBERT R, 61 39-50, 65 221-234, 66 666-679  
 EDWARDS, LYDIA B, 80 747-749  
 EDWARDS, PHYLLIS Q, 76 517-539, 77 546-550, 79 83-86  
 EFFLER, DONALD B, 63 252-254, 71 668-675, 775-784, 73 19-30, 75 469-475  
 EGAN, J B, 78 251-258  
 EHRENHAFT, J L, 72 801-809  
 EHRICH, JOHN, 63 4-6, 7-16  
 EICH, ROBERT H, 76 22-32, 77 863-866, 78 191-202  
 EICHENHOLZ, ALFRED, 71 473-502  
 EIDUS, L, 78 785-787, 79 816-817  
 EIDUSON, SAMUEL, 60 439-447, 448-454  
 EISENMAN, WILLIAM, 61 738-741  
 EISMAN, E A, 70 121-129, 130-138, 77 694-702, 703-711  
 ELIAS, FREDERICK, 66 750-757  
 ELKINS, CHARLES W, 63 227-229  
 ELLICOTT, MARJORIE F, 74 317-342  
 ELLIOTT, WILLIAM E, 69 604-611  
 ELLIS, CATHERINE, 74 (Supplement, August 232-240)  
 ELLIS, F HENRY, JR, 65 159-167, 74 581-589, 940-953  
 ELLISON, LOIS T, 80 181-187  
 ELLISON, OSCAR, 70 701-713  
 ELLISON, ROBERT G, 80 181-187  
 ELMENDORF, DUMONT F, JR, 65 429-442, 66 391-415, 70 228-265, 71 316-317  
 ELMORE, FRANCIS H, 61 95-105, 106-115  
 EL NAGAH, A M, 79 119-133  
 ELOESSER, L, 73 444-445  
 ELSBERG, SANFORD S, 65 655-672, 74 84-91  
 EMERSON, GEORGE L, 65 210-214  
 EMMART, E W, 59 438-448 63 100-107, 68 220-228

ENG, R TAK, 72 356-366  
 ENGBAER, HANS CHR, 75 347-348  
 ENGEL, D, 68 940-941  
 ENGELHARD, WARREN E, 76 279-285  
 ENTERLINE, PHILIP E, 66 548-566, 70 593-600  
 EPSTEIN, ISRAEL G, 75 553-575, 78 815-821  
 EPSTEIN, JOSEPH G, 68 796-798  
 EPSTEIN, LAZAR, 66 90-94  
 ERLENMEYER, H, 67 629-643  
 ERLER, STANLEIGH, 69 1037-1041  
 ERLICH, HENRY, 61 563-568  
 ERSKINE, FREDERICK A, 59 128-139  
 ERVIN, JOHN R, 71 775-784  
 ESCOVITZ, WILLIAM E, 66 373-377  
 ESLAMI, VALI, 78 127-130  
 EVANDER, L C, 78 637-643  
 EVANS, ELWYN, 61 335-345  
 EVANS, J R, 69 464-468  
 EVANS, JOHN A, 60 487-500  
 EVANS, ROBERT L, 70 296-303

## F

FABRICANT, CATHERINE G, 66 567-577  
 FABRICANT, JULIUS, 66 567-577  
 FABRIZIO, ANGELINA M, 65 250-271, 66 314-334  
 FAHLBERG, WILLSON J, 76 896  
 FALK, ABRAHAM, 64 159-169, 66 228-232, 357-363, 509-521, 68 177-187, 70 689-700, 74 367-375, 897-902  
 FALOON, WILLIAM W, 68 207-211  
 FALOR, WILLIAM H, 70 166-170  
 FARBER, JASON E, 62 109-111, 63 67-75  
 FARID, Z, 79 119-133  
 FAUCHER, I O, 73 576-580, 75 670-674  
 FAVEZ, G, 80 26-37  
 FAVOUR, CUTTING B, 60 212-222, 72 577-600, 73 581-585  
 FEINBERG, RICHARD J, 67 103-105  
 FEIND, CARL R, 60 39-44  
 FELD, DAVID D, 59 317-324  
 FELDMAN, JOSÉ, 74 153-159  
 FELDMAN, WILLIAM H, 62 149-155, 345-352, 66 477-485, 722-731, 67 341-353, 68 75-81, 575-582, 69 859-868, 71 752-754, 75 266-279  
 FELDMANN, FLOYD M, 61 892, 63 721, 71 140-143  
 FELLOWS, HYNES HAROLD, 60 487-500  
 FELTON, FRANCES G, 80 267-268  
 FENGER, E P K, 59 113-127, 78 106-110  
 FENNER, FRANK, 63 714-716, 64 353-380, 68 321-341, 342-371, 73 650-673, 76 76-89  
 FERARU, FELIX, 79 577-590  
 FEREBEE, SHIRLEY H, 66 632-635, 67 108-113, 539-543, 68 264-269, 70 521-526, 73 1-18, 74 917-939, 80 371-387  
 FERGUS, EMILY B, 79 659-662  
 FERNÁNDEZ, MARTHA, 73 61-71  
 FERRER, M IRENÉ, 80 510-521

- FETTER, B F , 70 498-503  
 FETTERHOFF, K I , 66 501  
 FIDLER, W F , 64 307-312  
 FILLEY, GILES F , 80 (Supplement, July 213)  
 FINESTONE, ALBERT J , 64 630-644  
 FINKBINER, RODMAN B , 75 122-134  
 FINLAY, A C , 63 1-3  
 FIORE, JOHN M , 74 289-292  
 FIRESTONE, GEORGE M , 59 415-428  
 FISCHER, D ARMIN, 78 604-609  
 FISCHER, HERBERT K , 76 880-887  
 FISH, CHARLES H , 65 187-193  
 FISHER, BRUCE M , 64 557-563  
 FISHER, DON L , 73 134-138  
 FISHER, HYMAN, 61 257-262  
 FISHER, MYRON W , 66 626-628, 753-761, 69 469-470, 797-805  
 FISHLER, J STUART, 62 144-148  
 FITE, G L , 68 220-228  
 FITZPATRICK, FLORENCE K , 68 451-454, 77 867-868  
 FITZPATRICK, MARTIN J , 69 370-382, 72 675-684, 77 387-399  
 FITZPATRICK, WILLIAM J , 60 660-669  
 FJELDE, AUDREY L , 75 347-348  
 FLEISCHNER, FELIX G , 62 45-57  
 FLETCHER, C M , 80 483-494  
 FLOREI, M ETHEL, 65 547-571, 73 818-830  
 FLYNN, PAUL F , 69 50-57  
 FOGARTY, JOHN E , 78 661-666  
 FOLEI, JOHN A , 74 277-283  
 FOLTZ, ELDON L , 74 835-855  
 FORD, RALPH V , 68 541-547  
 FORD, WILLIAM B , 73 134-138  
 FORDHAM, GEORGE F , 62 428-433  
 FORNEY, JOHN E , 69 241-246  
 FORREST, ELIZABETH S , 68 786-787, 80 744-746  
 FORSE, MAX A , 78 268-273  
 FOURNIER, ETIENNE, 66 382-383  
 FOWLER, EDMUND P , Jr , 60 39-44  
 FOWLER, WARD S , 72 783-800, 80 (Supplement, July 118-120)  
 FOX, JOHN A , 75 584-587  
 FOX, R T , 78 822-831  
 FOX, THEODORE H , 60 249-257  
 FOX, WALLACE, 71 314-315, 317-318  
 FRANCIS, JOHN, 73 276-290, 748-763  
 FRANK, BERNARD, 73 966  
 FRANK, N ROBERT, 67 568-597, 755-778, 71 676-692, 80 806-824  
 FRAPPIER, ARMAND, 79 296-306  
 FRASER, RICHARD S , 75 999-1002  
 FRAWLEY, THOMAS F , 70 841-851  
 FREED, C C , 76 398-409  
 FREEDMAN, BENJAMIN, 60 258-263  
 FREIMAN, DAVID G , 59 449-460  
 FREMMING, BENJAMIN D , 72 204-209, 76 225-231  
 FREMONT, R E , 63 591-596  
 FREMONT-SMITH, PAUL, 60 212-222  
 FREUND, JULIUS, 79 87-89  
 FREY, W H , 60 269-271  
 FRIEDLANDER, RALPH, 60 189-205  
 FRIEDMAN, ALAN J , 77 338-345  
 FRIEDMAN, BERNARD L , 79 265-272  
 FRIEDMAN, ELI, 60 354-358, 61 442  
 FRIEDMAN, EMANUEL, 72 833-839  
 FRIEDMAN, LORRAINE, 74 147-148, 245-248  
 FRIEDMAN, MAX M , 63 213-219, 64 448-452  
 FRIEDMAN, NATHAN, 76 123-131  
 FRIEDRICH, T , 79 351-356  
 FRISCH, ARTHUR W , 64 551-556, 65 278-288, 289-301, 302-315  
 FRITTS, HARRY W , Jr , 80 (Supplement, July 131)  
 FROBISHER, MARTIN, Jr , 60 621-627, 67 497-502, 530-534, 68 419-424  
 FROEB, HERMAN F , 77 737-748  
 FROELICH, ERNEST J , 78 74-82  
 FROMAN, SEYMOUR, 76 435-450, 964-969, 77 1030-1032  
 FROSTAD, SIMON, 79 597-605  
 FRUHLINGER, BEN, 68 42-47  
 FRY, DONALD L , 80 (Supplement, July 123-125)  
 FRY, LOIS, 73 547-562  
 FRY, WESLEY, 71 30-48  
 FUJIKAWA, Y FRED, 66 246-250  
 FUJITA, YUTAKA, 78 884-898  
 FUNK, V K , 59 113-127  
 FURCOLOW, MICHAEL L , 64 468-469, 68 307-320, 69 234-240, 73 609-619, 75 938-948, 78 667-681  
 FUSIA, DONALD A , Jr , 65 744-753  
 FUSILLO, M , 69 464-468  
 FUSILLO, MATTHEW H , 75 949-953, 954-957, 76 507-508, 78 793
- ## G
- GABY, WILLIAM L , 65 272-277, 67 657-664  
 GAENSLER, EDWARD A , 62 17-28, 63 547-555, 64 256-278, 67 3-21, 568-597, 755-778, 779-797, 74 317-342, 75 730-744, 80 (Supplement, July 185-193)  
 GAFFNEY, ETHNA E , 71 785-798, 799-809  
 GAGE, ROBERT P , 69 78-83, 70 899-900, 73 52-60  
 GAGLIARDO, FRANK J , 64 675-681, 66 762-764  
 GAHWYLER, MAX, 72 659-662  
 GAINER, JOSEPH H , 62 149-155, 345-352, 63 36-43  
 GALBRAITH, ELIZABETH H , 71 596-599  
 GALE, DAVID, 73 139-141, 77 1005-1011, 1012-1016, 80 95-99  
 GALE, GODFREY L , 66 732-743, 70 610-622, 75 410-419  
 GALE, JOSEPH W , 59 10-29, 62 543-548, 74 977  
 GALIHER, CLAUDIA B , 59 494-510  
 GALLAHER, B SHANNON, 80 181-187  
 GANCEDO, HECTOR A , 71 668-675  
 GANS, ROBERT H , 62 360-373

- GARATTINI, S, 80 110-111  
 GARBINSKI, TADEUSZ, 77 1026-1029  
 GARCIA RAMOS, J, 71 822-829, 73 519-528  
 GARGINKEL, LAWRENCE, 76 988-1001  
 GARGULAS, A, 76 263-271  
 GARLAND, L H, 64 225-248  
 GARMENT, EDWARD M, 68 796-798  
 GARROD, LAWRENCE P, 62 582-585  
 GARTHWAITE, BETTINA, 69 520-542  
 GASS, R S, 65 111-127, 70 360-362, 1009-1019, 75 111-121  
 GASTAMIDE-ODIER, M M, 75 843-845, 77 662-668, 79 94  
 GEBAUER, PAUL W, 62 176-189, 80 6-11  
 GEEVER, ERVING F, 61 422-425, 66 680-698  
 GEIB, PHILIP O, 72 257-267  
 GEMMILL, C L, 79 339-343  
 GENSINI, GOFREDO, 80 1-5  
 GENTRY, W HAROLD, 66 95-98, 71 319  
 GERBEAUX, J, 80 326-339  
 GERE, J BREWSTER, 76 988-1001  
 GERONIMUS, LIPPMAN H, 65 520-533  
 GERSON, CHARLES E, 64 686-690  
 GERSTL, B, 72 345-355, 79 212-220  
 GETZ, HORACE R, 60 439-447, 448-454, 64 381-393, 72 218-227, 73 603-604  
 GILBERT, ROBERT, 76 22-32, 77 863-866, 78 191  
 GILBOY, JAMES T, 66 233-239  
 GILMAN, RICHARD A, 70 734-738, 74 874-884  
 GINSBURG, BEN, 75 688-691  
 GISI, T A, 77 694-702, 703-711  
 GITTENS, S AUBREY, 69 673-681, 79 307-314  
 GLASER, STANLEY, 79 427-439  
 GLASS, MACELLIS, 73 110-116  
 GLASS, R, 69 1057-1058  
 GLICK, MARY CATHERINE, 68 625-628  
 GLICKLICH, MARVIN, 71 573-583  
 GODDARD, JEAN, 69 595-598  
 GOLBERG, MAURICIO, 74 (Supplement, August 267-278)  
 GOLDBERG, JACOB, 60 189-205  
 GOLDBERG, S I, 69 1057-1058  
 GOLDMAN, ALFRED, 70 285-295, 76 123-131  
 GOLDMAN, DEXTER S, 73 674-680  
 GOLDMAN, ELISE CARR, 73 674-680  
 GOLDMAN, H I, 76 398-409, 79 457-467  
 GOLDMAN, HOWARD L, 77 923-930  
 GOLDMAN, HYMIE, 77 209-220  
 GOLDMAN, MILTON, 70 149-154, 72 863-865, 76 909-911  
 GOLDNER, MARTIN G, 65 589-595  
 GOLDSMITH, JOHN R, 78 180-190  
 GOLDSTEIN, GERALD, 74 783-792  
 GOLDSTEIN, MERRILL M, 74 210-219, 220-228, 77 1-9  
 GOLLEY, PAUL M, 60 377-382  
 GOLOMB, JOSEPH, 62 441-445  
 GOMEZ, FERNANDO D, 66 1-15  
 GOMORI, GEORGE, 59 554-561, 61 560-562  
 GONZALEZ-MENDOZA, AMADO, 77 543-545, 79 246-250  
 GORDON, ARMOND, 64 50-63  
 GORDON, BURGFSS, 59 270-288, 61 201-225, 65 24-47  
 GORDON, EDWARD E, 71 722-731  
 GORDON, JOSEPH, 67 29-44  
 GORDON, LEE, 72 64-70  
 GORELICK, DAVID F, 63 346-354  
 GOTSHALL, R Y, 62 475-480  
 GOULD, DAVID M, 77 375-386  
 GOULD, WILBUR J, 59 679-686  
 GOZSY, BÉLA, 73 442-443, 75 684-687  
 GRADY, EDGAR D, 63 526-537  
 GRANT, I W B, 74 485-510  
 GRANVILLE, GEORGE E, 68 727-733  
 GRASSET, EDMOND, 64 695  
 GRAUB, MILTON, 61 735-737  
 GRAY, DAVID F, 65 572-588, 68 82-95, 69 92-103, 991-1001, 72 171-195, 75 519-520, 78 226-234, 235-250  
 GRAY, J A C, 75 833-835  
 GRAY, J E, 77 976-982  
 GRAYSTON, J THOMAS, 68 307-320  
 GRAYZEL, DAVID M, 60 801-807  
 GREEN, JOSEPH M, 72 633-646  
 GREEN, ROBERT A, 79 790-798, 80 65-70, 833-844, 895-901  
 GREENBERG, L, 78 785-787, 79 816-817  
 GREENBERGER, MONROE E, 61 508-517  
 GREER, J W, 79 119-133  
 GREGG, ALAN, 67 517-521  
 GREGOIRE, F, 71 867-876  
 GREGORY, FRANCIS J, 60 366-376, 65 718-721  
 GREGORY, LLOYD J, 69 58-64  
 GRIBKOFF, GEORGE P, 70 916-919  
 GRIFFIN, VIRGINIA L, 77 356-358  
 GRIFFITH, LEWIS J, 74 462-463  
 GRIFFITH, ROBERT L, 70 1020-1029  
 GRIGG, E R N, 78 151-172, 426-453, 583-603  
 GROSS, JOHN H, 77 506-510  
 GROVES, LAURENCE K, 73 19-30  
 GROW, J B, 70 1030-1041, 71 390-405  
 GRUMBACH, FRANÇOISE, 79 1-5  
 GRUNBERG, E, 67 674-675, 68 277-279, 71 898-899  
 GRZYBOWSKI, STEFAN, 72 398-402, 73 305, 75 432-441  
 GUILLAUME, ROBERT L, 69 745-758  
 GULD, JOHANNES, 72 126-128, 74 297-303, 80 255-256  
 GUNN, F D, 61 77-94  
 GUPTA, K C, 70 328-333, 73 294-295, 296-300  
 GUTEKUNST, R A, 62 116-117  
 GUTHEIL, DOUGLAS, 62 645-653  
 GUTHRIE, GEORGE, 67 432-439  
 GUTIÉRREZ-VÁZQUEZ, J M, 74 50-58  
 GYARFAS, WILLIAM, 70 285-295

## H

- HAAPANEN, JAAKKO H , 80 1-5  
 HAAS, ALBERT, 71 722-731  
 HABEEB, WILLIAM J , 61 323-334  
 HACKNEY, ROBERT L , 63 103-118  
 HAELIG, ARTHUR W , 76 140-143  
 HAIMSOHN, JAMES S , 69 443-450  
 HAKSTIAN, A , 70 535-536  
 HALEY, L D , 70 912-915, 74 249-257  
 HALEY, RAPHAEL R , 66 58-62, 69 543-553  
 HALL, H E , 75 807-822, 76 888-891, 77 815-822  
 HALL, WENDELL H , 74 478-480, 773-782, 79 518-521  
 HALLE, SHEA, 62 213-218  
 HALLETT, WILBUR Y , 80 716-723  
 HALLEY, T V , 63 44-48  
 HALPERN, B , 70 665-671  
 HALPERT, BELÁ, 64 170-181, 68 727-733, 71 762-764  
 HAMBLETON, ARTHUR, 75 1007-1008, 76 159-160  
 HAMILTON, MARY ALICE, 66 680-698, 77 436-449, 79 221-231  
 HAMILTON, W F , 60 501-513, 80 181-187  
 HAMILTON, WILLIAM F , Jr , 80 181-187  
 HAMMARSTEN, JAMES F , 78 391-398, 79 606-611  
 HAMMEL, JOSEPH V , 80 915-918  
 HAMRE, D , 66 219-227  
 HAN, EUNG SOO, 68 583-593  
 HAND, ETHEL M , 60 773-787  
 HANDY, VINCENT H , 59 78-85  
 HANKEY, LILLIAN, 66 378-380  
 HANKS, JOHN H , 69 173-191, 74 597-607, 608-615, 77 789-801  
 HANLON, C ROLLINS, 65 48-63  
 HANSON, MARK, 64 159-169  
 HARDEN, K ALBERT, 63 103-118, 70 701-713  
 HARDY, ALBERT V , 80 188-199  
 HARDY, HARRIET L , 68 941-942, 72 129-132, 74 885-896  
 HARDY, KENNETH L , 73 451-471  
 HARENESS, J T , 61 443-464, 64 225-248, 249-255  
 HARRELL, DICK, 67 671-673  
 HARRELL, W K, 69 505-510  
 HARRIS, ALBERT H , 76 426-434  
 HARRIS, H WILLIAM, 71 126-130, 78 682-691, 944-948, 79 663-665  
 HARRIS, LEONARD C , 74 (Supplement, August 246-255)  
 HARRIS, MARVIN S , 76 123-131, 77 338-345  
 HARRIS, MILFORD D , Jr 76 225-231  
 HARRIS, T N , 59 186-197  
 HARRISON, HARLON W , 69 554-565  
 HARROWER, J ROBERTS, 68 286-289, 73 593-596, 76 892-895  
 HART, P D'ARCY, 59 223-239  
 HARVEY, H P B , 77 492-495  
 HARVEY, RÉJANE M , 80 510-521  
 HARVEY, SIDNEY D , 74 533-540  
 HASENCLEVER, H F , 72 687-689  
 HASSERT, G LEE, JR , 65 392-401  
 HATCH, H B , Jr , 76 291-297  
 HATCH, HAROLD S , 67 232-246, 68 782-785  
 HAUG, WALTER A , 78 268-273  
 HAUSER, GEORGE, 69 334-350  
 HAUSMANN, PAUL F , 63 210-212  
 HAVERLAND, HARRY W , 74 112-116  
 HAWKINS, NORMAN G , 75 768-780  
 HAWLEY, WILLIAM L , 75 145-147, 76 906-908  
 HAYASHI, MITSUO, 79 371-373  
 HAYES, J N , 62 (Supplement, July 90-97)  
 HAYES, J W , 69 845-846  
 HAYRABETIAN, BERDJ, 68 165-176  
 HAZLEHURST, GEORGE N , 71 1-11, 12-29  
 HEAD, JEROME R , 60 1-14  
 HECKEL, JOHN, 69 307-308  
 HECKLY, ROBERT J , 61 798-808, 62 99-100, 63 718-720, 64 602-619  
 HEDBERG, GUSTAF A , 61 193-200  
 HEDGECOCK, LOYD W , 73 576-580, 75 670-674, 77 93-105  
 HEIKEN, CHARLES A , 63 480-486  
 HEKI, SHINICHIRO, 77 529-535  
 HELLER, ALFRED, 75 71-82  
 HELLER, M L , 75 730-744  
 HELLER, PAUL, 61 868-874  
 HEMANS, MARGARET J , 66 351-356  
 HEMINGWAY, ALLAN, 76 195-214  
 HEMPHILL, ROGER A , 66 261-270  
 HENDERSON, ALFRED R , 60 811  
 HENDERSON, HOWARD J , 64 381-393, 71 609-616  
 HENDERSON, RUTH W , 80 398-403  
 HENSLER, NESTOR M , 76 132-139, 78 8-16  
 HENTEL, WILLIAM, 61 369-386, 63 476-479  
 HEPLAR, JOSEPH Q , 67 669-670  
 HEPPLESTON, A G , 59 198-218, 61 765-797  
 HERBEN, G F , 66 605-614  
 HERBUT, PETER A , 61 60-65  
 HERR, ROSS R , 75 584-587  
 HERRERA, VIVENCIO A , 74 277-283  
 HERRING, JACK L , 79 251-252, 531-532  
 HERSCHFUS, J A , 69 915-929  
 HERTZBERG, GERHARD, 62 118-119  
 HERTZMAN, VICTOR O , 65 443-450  
 HESS, ADELINE R , 62 481-483, 64 516-519, 73 892-906, 75 678-683  
 HEUCK, JULIA, 66 548-566  
 HEWELL, BARBARA, 69 733-744, 70 1064-1082  
 HEWITT, WILLARD C , 69 1054-1056  
 HICKAM, JOHN B , 74 309-316, 343-350, 78 1-7  
 HIGH, ROBERT H , 74 (Supplement, August 256-266)  
 HIGHTOWER, JOHN A , 69 58-64  
 HILL, GILBERT A , 75 849-850  
 HILL, HARRY E , 62 1-7, 76 132-139, 78 8-16  
 HILL, IDA, 63 487-489  
 HILLIS, B R , 74 485-510



- HILTZ, D M , 61 355-368  
 HILTZ, J E , 79 468-473  
 HIMMELSTEIN, AARON, 63 231-251, 64 583-601, 67 154-172  
 HINSHAW, H CORWIN, 59 140-167, 60 32-38, 61 145-157, 443-464, 64 225-248, 557-563, 68 263, 70 9-14, 71 752-754, 74 142-144  
 HINSON, K F W , 68 739-745  
 HIRSCH, A , 75 793-806  
 HIRSCH, JAMES G , 70 312-319, 955-976, 977-988, 989-994, 71 447-451, 732-742, 894-897, 75 331-337, 359-409  
 HITE, K EILEEN, 70 178, 219-227  
 HOBBY, GLADYS L , 59 219-220, 60 808-810, 63 1-3, 17-24, 434-440, 65 754-774, 67 808-827, 68 292-294, 69 173-191, 70 191-218, 527-530, 71 457-458, 72 367-372, 386-389, 846-850, 76 1031-1048, 78 934-938, 939-943, 80 274-276, 415-423  
 HOBSON, LAWRENCE B , 62 128-143  
 HOCHBERG, LEW A , 63 150-175  
 HOCHSTEIN, F , 63 1-3  
 HOCOTT, JOE B , 80 (Supplement, July 45-48)  
 HODGE, HAROLD C , 76 1063-1070  
 HOFFMAN, JOSEPH, 63 202-209  
 HOFFMAN, STANLEY H , 59 539-553  
 HOFFMANN, RICHARD, 67 798-807, 75 169-179  
 HOFMANN, GERALD N , 64 682-685  
 HOLDEN, H M , 60 654-659  
 HOLDING, BRUCE F , JR , 71 291-294  
 HOLIN, SABINE M , 79 427-439  
 HOLLAND, ROBERT H , 73 123-127  
 HOLLANDER, A GERSON, 67 497-502, 72 345-355, 438-551, 79 212-220  
 HOLLIFIELD, W C , 80 587-589  
 HOLLOWAY, JAMES B , JR , 60 228-235  
 HOLM, JOHANNES, 79 690-694  
 HOLMES, C X , 66 501  
 HOLMES, THOMAS H , 69 351-369, 73 795-804, 75 768-780  
 HOLMGREN, NELDA B , 59 102-105, 66 416-435  
 HOLZBERGER, PHILIP, 69 205-215  
 HONSKA, WALTER L , JR , 79 606  
 HOOD, R MAURICE, 78 21-37  
 HOPKINS, FREDERICK D , 65 494-503  
 HOPWOOD, LOUISE, 74 917-939  
 HORAVA, ALEXANDER, 67 677-678  
 HORNE, N W , 68 400-410  
 HOROWITZ, ISAAC, 63 346-354  
 HORSFALL, FRANK L , JR , 80 315-325  
 HORSMAN, R K , 63 476-479  
 HORTON, GLENN E , 69 443-450, 73 704-715, 78 135-137, 80 724-731  
 HORTON, RALPH, 62 572-581, 66 16-27 68 238-248, 71 193-200, 72 242-244, 77 413-417  
 HORWITZ, OLE, 80 659-675  
 HOSTY, THOMAS S , 78 576-582  
 HOUGLUM, BURTON, 69 406-418  
 HOUSTON, CHARLES, 80 (Supplement, July 213)  
 HOWARD, O P , 69 307-308  
 HOWARD, W LEONARD, 60 794-800, 63 140-149, 67 292-298, 70 518-520, 533-534, 71 766  
 HOWELL, JULIAN, 78 576-582  
 HOWLETT, KIRBY S , JR , 59 402-414, 63 312-324, 65 235-249, 68 270-272  
 HOYT, ANSON, 70 916-919, 75 618-623, 624-629, 76 752-760, 80 216-222  
 HSIE, JEN-YAH, 62 286-299  
 HSIUNG, G D , 70 912-915, 74 249-257  
 HUDGINS, PAUL C , 65 596-602, 603-611, 72 117-118, 340-344, 685-686, 856-858, 73 246-250, 75 83-92, 630-637, 78 138-139, 79 323-328, 382-383  
 HUDSON, HOLLAND, 66 104-108, 67 698-703  
 HUERGA, J DE LA, 77 120-133  
 HUGGIN, PERRY M , 79 204-211  
 HUGHES, FREDERIC J , JR , 63 295-311  
 HUGHES, HETTIE B , 67 798-807, 70 266-273  
 HUGHES, P G , 73 930-939  
 HUMPHREY, HAROLD I , 76 144-151  
 HUNTER, DON, 62 525-531  
 HUPPERT, MILTON, 76 451-467, 468-479, 77 1030-1031  
 HUPPLER, EDWARD G , 73 52-60  
 HURST, ALLAN, 64 489-498, 80 (Supplement, July 179-180)  
 HURWITZ, CHARLES, 62 87-90, 91-98, 638-644, 63 568-578, 68 127-135  
 HUSSEINI, HAIDAR, 65 655-672  
 HUTCHESON, R H , 65 111-127, 75 111-121  
 HUTCHINSON, JOANNE, 76 899-901  
 HUTCHISON, DORRIS, 60 78-89  
 HUIWARA, TOMEZO, 73 563-570  
 HWA, EUGENE C , 73 681-689  
 HYATT, ROBERT E , 80 (Supplement, July 138)  
 HYDE, BERNARD, 59 619-623, 61 883-886, 63 417-426  
 HYDE, LEROY, 59 619-623, 61 883-886, 62 525-531, 63 417-426, 69 1045-1050, 71 131-136, 78 906-915  
 HYMAN, GEORGE A , 59 539-553  
 HYMAN, MAURICE, 77 338-345  
  
 I  
 IBRAHIM, ABDULLA, 61 569-577  
 ILAND, C N , 68 372-381  
 ILASI, FRANK P , 66 436-448  
 ILAVSKY, JAN, 65 777-778, 69 280-286  
 INADA, KIYOSHI, 79 232-237  
 IRONSON, ELLIOTT, 70 806-811, 74 59-67, 72-77  
 IRVINE, K NEVILLE, 74 (Supplement, August 43-49)  
 ISAWA, YUKIO, 74 255-276  
 ISHAK, K G , 79 119-133  
 ISRAEL, HAROLD L , 62 408-417, 64 453-460, 67 671-673, 69 846-847  
 ITO, KAORU, 72 393-397, 76 90-102, 77 529-535

ITO, RIO, 67 526-529

IVANOVICS, GEORGE, 77 1017-1018

## J

JABLON, SEYMOUR, 73 620-636, 75 442-460, 76 517-539

JACK, ALEXANDER, 77 1005-1011, 1012-1016

JACKSON, E L, 60 62-77

JACKSON, EDITH R, 69 419-442

JACKSON, JOAN K, 79 659-662

JACOBS, LEWIS G, 71 437-440

JACOBS, SYDNEY, 59 76-77, 68 382-392, 70 304-311, 74 464-467, 79 105, 251-252, 531-532

JACOBSON, GEORGE, 69 940-956, 74 590-596

JACOBSON, H R, 63 587-590

JACOX, RALPH F, 60 541-546

JAFFÉ, FREDERICK A, 64 182-191

JAFFE, HENRY L, 60 249-257

JAHN, RICHARD P, 65 88-92, 66 244-245, 80 78-84

JAMBOR, WILLIAM P, 60 90-108, 109-120, 121-130, 67 354-365, 366-375

JAMES, E F, 71 321-323

JAMES, H A, 79 541

JAMES, LYNN A, 63 275-294

JAMES, VETILE D, 65 722-734

JAMESON, A GREGORY, 80 510-521

JAMESON, ELIZABETH L, 71 272-279

JANER, JOSÉ L, 67 132-153, 70 1099-1101

JANICKI, BERNARD W, 79 244-245

JANN, GREGORY J, 71 260-265, 266-271

JARROLD, THOMAS, 70 509-517

JEFFERIES, MILDRED B, 77 350-355, 79 669-671

JEKER, K, 79 351-356

JENKINS, BARBARA E, 68 264-269

JENKINS, DANIEL E, 64 170-181, 68 541-547, 727-733, 74 417-427, 468-470

JENKINS, JOHN T, 72 12-34

JENNINGS, A R, 61 399-406

JENNINGS, J C, 62 475-480

JENNINGS, PAMELA A, 72 171-195

JENNINGS, WILMA, 75 1003-1006

JENSEN, K A, 70 402-412

JENSEN, N KENNETH, 74 367-375

JOHNSEN, LYNN, 68 229-237, 69 1054-1056

JOHNSON, ALAN J, 76 1-21

JOHNSON, BERKLEY H, 61 578-581

JOHNSON, HENRY P, 75 139-144

JOHNSON, JANET J, 76 247-255

JOHNSON, JOAN M, 77 623-643

JOHNSON, JOHN E, JR, 66 497-500, 72 91-97

JOHNSON, J RICHARD, 70 623-636, 72 825-832

JOHNSON, LINDEN E, 67 299-321

JOHNSON, MAURINE P, 69 287-296, 980-990

JOHNSON, PEGGY M, 72 390-392, 863-865

JOHNSON, PHILIP C, 78 391-398

JOHNSON, RICHARD P, 59 656-663

JOHNSON, ROBERT S, 68 177-187, 70 296-303

JOHNSON, WILLIAM H, 73 99-109

JOHNSTON, DALE GORDON, 75 319-325

JOHNSTON, JOSEPH A, 74 (Supplement, August 173-182)

JOHNSTON, R N, 70 442-452, 78 932-933

JOHNSTONE, WENDYE E, 69 991-1001

JOINER, C L, 71 302-304

JOLLY, PAUL N, 60 589-603

JONES, AUDREY P, 70 266-273

JONES, EDNA M, 61 387-398, 60 533-534, 71 766

JONES, FRANCIS S, 68 657-677

JONES, JOHN C, 73 690-703

JONES, JULIA M, 73 229-238

JONES, MERRIAM J, 68 425-438, 439-443, 444-450

JONES, OSWALD R, 60 514-519

JONES, PERON O, 68 541-547, 74 417-427, 468-470

JONES, RALPH, JR, 63 672-673

JONES, ROBERT KNAPP, 74 802-806

JONES, RUSSELL S, 61 826-834, 63 381-398

JONES, WARREN, 63 459-469, 71 319

JONES, WILLIAM WILEY, 60 45-50

JORDAHL, CLARENCE, 75 659-666, 77 539-542, 80 431-433

JUAREZ, WILLIAM J, 76 468-479

JUHL, J W, 74 388-399

JUNGE, J M, 60 62-77

## K

KAHN, M T, 76 892-895

KAHN, MARCEL, 61 887-891

KALISH, CATHERINE, 65 187-193, 67 497-502

KALLQVIST, IVAR, 61 621-642, 64 430-441, 69 968-979, 73 40-51

KAMENER, ROBERT, 77 209-220

KANAI, KOOMI, 80 753-756

KANE, J H, 63 1-3

KANNER, O, 76 669-670

KANTOR, MILTON, 78 274-281, 524-535

KAPRAL, FRANK A, 78 712-724

KAPUR, VISHWA N, 80 269-273

KARA, CHARLES, 76 789-798

KARLSON, ALFRED G, 62 149-155, 62 345-352, 63 36-43, 427-433, 66 477-485, 722-731, 67 341-353, 68 75-81, 575-582, 70 531-532, 75 266-279, 78 753-759

KARNOFSKY, DAVID A, 69 957-962

KARNOSH, LOUIS J, 62 428-433

KARNOVSKY, MANFRED L, 71 609-616

KARNS, JAMES R, 79 746-755

KARPINOS, BERNARD D, 80 795-805

KASS, IRVING, 65 316-324, 74 796-797, 80 1-5

KASTL, WILLIAM H, 66 522-533

KASUGA, KAZUMI, 68 157-164, 799-802

KÁTÓ, LÁSZLÓ, 73 442-443, 75 684-687

KATO, MASAHIKO, 77 482-491, 80 240-248, 535-542

KATSUMURA, TATSUKI, 79 232-237

KATZ, EDWARD, 60 78-89

- KATZ, HARRY L, 61 835-844, 65 455-464, 589-595  
 KATZ, JULIUS, 61 51-56, 66 651-665, 67 279-285,  
 70 32-48, 73 31-39, 74 968-971, 862-870  
 KATZ, SOL, 68 760-770, 70 881-891, 74 106-111,  
 80 590-593  
 KAUFMAN, C J, 66 603-614  
 KAUFMAN, GERRARD, 68 21-30  
 KAUFMAN, JEROME E, 70 689-700  
 KAUFMAN, KIPSEL K, 66 211-215, 79 525  
 KAWAI, KENZO, 79 232-237  
 KAZIOWSKI, JOSEPH P, 73 266-275  
 KEE, JOHN L, JR, 76 970-982  
 KEEN, E N, 59 511-518  
 KEILER, ROBERT, 76 697-702  
 KELLEY, WINIFRED O, 65 83-87  
 KELLY, JACQUES M, 65 484-485  
 KELLY, MARGARET C, 68 564-574  
 KELLY, RUBY G, 61 269, 67 286-291, 68 583-593  
 KENDIG, EDWIN L, JR, 61 747-750, 70 161-165,  
 73 99-109, 74 119-151, 77 118-122  
 KENDIG, ISABELLE V, 73 138-141  
 KENNEDY, B R, 61 113-164  
 KENNEDY, H E, 77 802-814, 78 799-801  
 KENNEDY, R S, 68 100-110  
 KENNEL, MICHAEL, 70 149-154, 72 390-392, 863-865  
 KENT, DONALD C, 80 806-821  
 KENT, EDWARD M, 60 699-705, 73 134-138  
 KENT, G, 77 931-939  
 KERGIN, FREDERICK G, 66 732-743  
 KERNAN, PHILIP, 73 620-636, 75 412-460  
 KESCHNER, HAROLD W, 68 136-143  
 KESSLER, BRUCE J, 63 202-209  
 KHAN, I, 79 474-483  
 KHUNDKAR, A M, 78 117-120  
 KILBOURN, PHILIP C, 60 564-575  
 KILBURN, KAYE H, 80 411-442  
 KING, COLEMAN T, 75 199-222  
 KING, DONALD S, 60 536-538  
 KING, EDWARD J, 80 895-901  
 KING, ERNEST Q, 60 564-575  
 KINGSLEY, GEORGE R, 77 181-183  
 KINNEAR, A A, 59 511-518  
 KINSELL, LAURANCE W, 66 542-547  
 KINSELLA, T J, 59 113-127  
 KIRBY, WILLIAM M M, 60 343-353, 64 71-76,  
 69 625-630, 80 716-723  
 KIRCHHEIMER, WAIDEMAR F, 62 481-483, 64  
 516-519, 66 486-496, 758-761, 68 629-630, 70  
 665-671, 920-921, 71 743-751  
 KIRK, DANIEL L, 74 7-14  
 KIRMAN, DAVID, 77 184-188  
 KIRMSE, THOMAS W, 61 159-170  
 KIRSCHNER, PAUL A, 61 465-473  
 KIRSH, D, 72 345-355  
 KIRSHNER, J J, 78 474-477  
 KISER, J S, 65 511-518  
 KITAZAWA, YUKIO, 74 155-157, 79 329-338  
 KITCHELL, CYNTHIA L, 75 1003-1006  
 KITTEL, C FREDERICK, 77 387-399  
 KLASSON, KARL P, 66 699-721, 74 874-884, 77  
 62-72  
 KILIN, G C, 60 621-627, 63 159-169  
 KLEIN, SARAH, 68 290-291, 69 1022-1028, 74 428-  
 437  
 KNIGMAN, ALBERT M, 63 441-448, 672-673, 674-678  
 KLOPFENSTEIN, MORRIS D, 69 451-454, 70 533-  
 534, 71 766  
 KLOPFER, ROBERT, 60 273-287, 73 831-852  
 KNABE, GEORGE, 66 567-577  
 KNABZUK, MICHAEL, 68 212-219  
 KNIGHT, RALPH A, 77 983-989, 78 944-948, 80  
 261-266  
 KNIGHT, VERNON, 77 134-145, 80 12-18, 443-444  
 KNOPF, LOUIS F, 66 522-533  
 KNOWLES, ROBERT G, 75 618-623, 624-629  
 KNOW, ROBERT, 73 726-734  
 KNUDSON, JACK R, 61 809-825  
 KNUDSON, KENNETH P, 71 280-290  
 KOCH, MARIE L, 73 773-775, 77 356-358  
 KOCH-WEISER, DIETER, 67 490-496, 70 784-792,  
 71 556-565, 75 71-82  
 KOEHLER, W L, 68 284-285  
 KOEHLER, A O, 75 843-845  
 KOLMER, JOHN A, 64 102-112  
 KONNO, KIYOSHI, 75 529-537, 77 669-674, 675-680,  
 79 810-812  
 KONOPKA, E A, 70 121-129, 130-135, 77 694-702,  
 703-711  
 KONTERWITZ, H, 69 1057-1058  
 KONWALER, BENJAMIN D, 78 906-915  
 KORY, ROSS C, 77 729-736  
 KOTT, THADDEUS J, 63 487-489, 65 194-200  
 KOURTI, H, 74 (Supplement, August 197-203)  
 KOVITZ, C, 70 465-475, 641-664  
 KRAFT, JOSEPH R, 59 259-269  
 KRAHL, VERNON E, 80 (Supplement, July 24-40,  
 158-167)  
 KRASNITZ, ALEXANDER, 68 249-252  
 KRASNOW, IRVING, 71 361-370, 76 435-450, 451-467,  
 77 1030-1031  
 KRAUS, WILLIAM, 79 731-737  
 KREHL, W, 76 692-696  
 KREININ, SIDNEY, 59 650-655  
 KREIS, B, 80 85-88  
 KREISEL, HERBERT, 67 286-291, 292-298  
 KRESS, MILTON B, 80 (Supplement, July 194-202)  
 KROHN, EDWARD F, 70 376, 74 808-809  
 KROSS, ISIDOR, 61 431-435  
 KRUEGER, ERICH, 62 654-666  
 KRUEGER, VICTOR R, 76 64-75  
 KRÜGER-THIEMER, ECKEHARD, 77 364-367  
 KU, HSIEN-CHIH, 60 483-486  
 KUBALA, EUGEN, 78 949-951  
 KUBICA, G P, 73 529-538  
 KUHN, D M, 69 464-468  
 KULISH, M, 60 223-227, 65 635-636

- KUNA, MARTIN, 64 577-578  
 KUNOFSKY, SOLOMON, 70 32-48, 73 31-39, 74 968-971, 78 862-870  
 KURTZKE, JOHN F, 70 577-592  
 KURUCZ, JANOS, 76 789-798  
 KURUNG, JOSEPH M, 65 181-186, 66 578-587, 76 671-674, 675-678, 679-689  
 KURZMANN, RUDOLF, 75 529-537, 77 669-674, 675-680  
 KUSCHINSKI, HERTA, 63 213-219  
 KUSHNER, DANIEL S, 76 103-107, 108-122, 80 434-437  
 KUSUNOSE, MASAMICHI, 80 240-248  
 KWIEK, STANISLAW, 80 257-258
- L**
- LACK, CHARLES H, 73 362-377, 378-389, 74 (Supplement, August 124-133)  
 LAFF, HERMAN I, 74 (Supplement, August 267-277)  
 LAFORET, EUGENE G, 77 716-718  
 LAING, W A R, 71 201-219  
 LAMBERT, H P, 80 648-658  
 LAMBIOTTE, LOUIS O, 59 289-310  
 LAMOTTE, IRENE F, 80 181-187  
 LANDIS, FRANCIS B, 80 249-254  
 LAND, JAMES J, JR, 73 795-804  
 LANG, LEONARD P, 59 270-288, 61 201-225  
 LANGMUIR, ALEXANDER D, 64 461-467  
 LANGTON, GERTRUDE K, 62 190-208  
 LARKIN, JOHN C, JR, 63 116-118, 69 443-450, 72 667-674, 843-845, 75 667-669, 78 135-137  
 LAROS, C D, 78 563-569  
 LARSEN, AUBREY B, 68 425-438, 439-443, 444-450, 77 177-180, 712-715  
 LARSEN, D H, 74 284-288  
 LARSH, HOWARD W, 75 938-948  
 LARSON, FRANK C, 70 102-108  
 LARSON, L M, 59 113-127  
 LASCHL, EUNICE M, 80 188-199  
 LATTIMER, JOHN K, 61 518-524, 66 744-749, 67 604-612, 69 618-624, 70 149-154, 76 909-911  
 LAUBACH, C A, JR, 60 1-14  
 LAUENER, H, 79 351-356, 80 26-37  
 LAURIE, J H, 62 331-332  
 LAVALLEE, A, 68 199-207  
 LAWRENCE, CARL A, 79 374-377  
 LAWRENCE, L THEODORE, 80 575-581  
 LAWRENCE, MONTAGUE S, 72 801-809  
 LAWRENCE, SANFORD H, 77 181-183  
 LAWSON, JOHN F, 59 687-691  
 LAWTON, ALFRED H, 80 915-918  
 LEACH, RONALD L, 68 321-341, 342-371  
 LECHEVALIER, HUBERT A, 67 261-264  
 LEDERER, E, 67 853-858  
 LEE, HENRY F, 61 738-741, 66 623-625  
 LEE, J ROBERT, 69 625-630  
 LEE, S C, 72 356-366  
 LEE, SEUNG HOON, 74 572-580, 76 1106-1109  
 LEECH, F B, 69 806-817  
 LEES, A W, 68 400-410, 78 769-772  
 LEES, T M, 63 1-3  
 LEES, WILLIAM M, 61 648-661, 78 822-831  
 LEFEBER, EDWARD J, 61 247-256  
 LEFTWICH, CHARLES I, 77 737-748  
 LEGOLVAN, P C, 79 119-133  
 LEHAN, PATRICK H, 75 938-948  
 LEHMAN, J STAUFFER, 69 657-672  
 LEIFHEIT, HOWARD C, 79 344-350  
 LEIFSON, EINAR, 75 148-152  
 LEIGHNINGER, DAVID S, 71 904-924  
 LEINER, GEORGE C, 61 868-874, 63 325-331, 65 465-476, 76 320-321, 80 902-903  
 LEISE, J M, 78 111-116  
 LEITES, VERA, 80 89-94  
 LEKOU, S, 76 263-271  
 LEMAISTRE, CHARLES, 64 295-306  
 LEMEUR, G, 79 6-18  
 LEMONDE, PAUL, 71 319-321  
 LENERT, TULITA F, 60 808-810, 63 1-3, 17-24, 434-440, 65 754-774, 68 292-294, 70 191-218, 527-530, 71 457-458, 72 367-372, 386-389, 846-850, 76 1031-1048, 78 934-938, 939-943, 80 274-276  
 LENNOX, R H, 74 (Supplement, August 160-168)  
 LEONARD, ALAN J, 68 382-392  
 LEONARDI, A, 80 110-111  
 LEPINE, LOUIS T, 73 438-441  
 LEPPER, MARK H, 69 192-204  
 LERNER, ERNEST N, 80 188-199  
 LESTER, CHARLES W, 64 691-694, 73 229-238, 78 399-402  
 LESTER, WILLIAM, 74 121-127, 77 462-472  
 LEUALLEN, EDMUND C, 72 783-801  
 LEVIN, NILS, 72 513-526  
 LEVINE, I, 69 1057-1058  
 LEVINE, MACY I, 59 701-706, 67 535-537  
 LEVINE, MILTON I, 62 118-119  
 LEVINE, MORTON, 75 517-518, 77 501-505  
 LEVY, DAVID, 79 666-668, 80 587-589  
 LEVY, F M, 79 484-491  
 LEVY, RICHARD S, 79 152-179, 180-203  
 LEW, JOON, 74 152  
 LEWIN, EDWARD, 71 447-451, 732-741  
 LEWIS, ALBERT G, JR, 80 188-199  
 LEWIS, EDWARD C, II, 74 438-440  
 LEWIS, GEORGE T, 66 378-380  
 LEWIS, W G, 61 881-882  
 LEWIS, WILLIAM C, 70 892-898, 71 419-428, 72 633-646, 73 338-350, 74 964-967, 77 311-322  
 LEWKOWICZ, STEPHANIE, 74 15-28  
 LIACACOS, D, 74 (Supplement, August 197-208), 76 263-271, 79 522-524  
 LIBERMANN, DAVID, 79 1-5  
 LICHTENSTEIN, HERMANN, 69 837-840

- LICHTENSTEIN, LOUIS, 60 249-257  
 LICHTENSTEIN, MEYER R, 60 576-588, 64 77-80,  
 66 161-171, 68 229-237, 69 217-260, 71 961-963  
 LILBERMAN, J E, 59 138-448  
 LIEBOW, AVRILL A, 80 (Supplement, July 67-91)  
 LIMES, BARNEY J, 79 606-611  
 LIN, T K, 77 387-399  
 LINCOLN, ARTHUR F, 75 999-1003, 77 536-538  
 LINCOLN, EDITH M, 61 159-170, 64 499-507, 66  
 63-76, 67 732-754, 69 682-689, 73 940-943, 74  
 15-28, (Supplement, August 246-255), 75  
 594-600, 76 588-600, 77 39-61, 271-289, 79  
 31-40  
 LINCOLN, N STANLEY, 62 572-581, 66 16-27, 68  
 238-248, 70 15-31, 71 193-200, 519-528, 72  
 242-244, 77 413-417  
 LINDEN, IRWIN H, 69 116-120  
 LINDGREN, INGA, 80 (Supplement, July 185-193)  
 LINDH, HOWARD, 65 511-518  
 LINDSAY, STUART, 66 77-85  
 LINDSEY, ERICKA, 73 581-585  
 LINDSKOG, GUSTAF E, 63 579-586, 70 155-160  
 LINEBERRY, WILLIAM T, JR, 61 426-430  
 LINELL, MICHAEL A, 74 410-416, 76 636-642  
 LINKER, MATTHEW, 62 441-445  
 LINN, RICHARD H, 70 1020-1029, 72 663-666,  
 74 464-467, 622-623, 79 251-252, 531-532  
 LISA, JAMES R, 63 202-209  
 LITTLE, MARSHALL S, 75 145-147, 76 906-908  
 LITZENBERGER, WILLARD L, 69 443-450  
 LIU, KUANG-YUAN, 60 483-486  
 LIVINGS, DOROTHY G, 70 637-640, 72 756-782  
 LOCKE, BEN Z, 70 32-48, 73 31-39  
 LOCKHART, ELIZABETH A, 80 95-99  
 LOGAN, P L, 71 830-840  
 LONG, ESMOND R, 59 481-493, 60 527-531, 62  
 (Supplement, July 3-12), 63 355-359, 64 381-  
 393, 65 494-503, 69 631-633, 70 383-390, 71  
 609-616, 75 852-855, 78 499-511  
 LOOSLI, CLAYTON G, 80 (Supplement, July 5-20)  
 LÓPEZ MAJANO, VICENTE, 72 537-538  
 LORBER, JOHN, 69 13-25, 78 38-61, 101-105  
 LORENZ, THOMAS H, 66 449-456, 70 892-898,  
 71 419-428, 72 633-646, 73 338-350  
 LORRIMAN, GERARD, 79 756-763  
 LOTT, WILLIAM A, 65 357-364, 67 354-365, 366-375  
 LOUDON, R G, 77 623-643  
 LOVEJOY, FRANK W, JR, 59 364-369, 62.29-44  
 LOVELOCK, FRANCIS J, 72 390-392  
 LOW, EUGENE, 79 612-621  
 LOWE, E P, 70 498-503  
 LOWELL, ANTHONY M, 72 419-452  
 LOWELL, FRANCIS C, 80 (Supplement, July  
 181-183)  
 LOWELL, JAMES R, 78 391-398  
 LOWELL, LAWRENCE M, 68 885-901  
 LOWENSTEIN, BERNARD, 72 373-380, 74 977  
 LOWRI, HOPE, 60 51-61  
 LU, F C, 68 199-207  
 LU, SUNG-NIEN, 62 360-373  
 LUBING, HAROLD N, 68 458-461  
 LUCAS, E H, 62 475-480  
 LUFT, ULRICH C, 72 465-478  
 LUKAS, DANIEL S, 64 279-294  
 LULL, GEORGE F, JR, 79 641-651  
 LUNN, JOSEPH, 79 72-77  
 LUPINI, BELARDINO, 79 307-314  
 LURIDIANA, NIVEO, 73 785-786  
 LURIE, MAX B, 59 1-9, 168-185, 186-197, 198-218,  
 61 765-797, 67 265-266, 69 1059-1060, 72 297-  
 329, 73 434-437, 79 152-179, 180-203  
 LUTZ, W, 77 400-412  
 LYNCH, HELEN P, 67 106-107, 69 307-308, 77  
 1023-1025  
 LYNCH, WILLIAM J, 68 229-237  
 LYON, RICHARD H, 76 247-255, 79 518-521  
 LYONS, HAROLD A, 64 327-352, 71 635-667  
 LYTCHOTT, GEORGE I, 73 940-943, 75 135-138
- ## M
- MA, JOHN, 74 457-461  
 MA, Y Y, 59 519-538  
 McALISTER, ELIZABETH, 79 669-671  
 McAULIFFE, WILLIAM J, 60 524-526  
 McCLELLAN, MARVIN, 70 1064-1082  
 McCLEMENT, JOHN H, 63 231-251, 64 583-601,  
 67 154-172  
 McClosky, E T, 59 438-448  
 McCord, DON L, 78 21-37  
 McCormack, LAWRENCE J, 71 668-675  
 McCormick, GEORGES F, 68 760-770, 70 881-891  
 McCoy, HERBERT T, 62 227, 353-359  
 McCuiston, C FRED, 76 480-490  
 McCune, ROBERT M, JR, 69 319-333, 70 743-747,  
 72 851-855, 74 471-473, 572-580, (Supplement,  
 August 100-108), 75 659-666, 76 1100-1105,  
 1106-1109  
 MacCurdy, JOE M, 66 497-500  
 MacDERMOT, P N, 76 832-851  
 McDermott, WALSH, 61 145-157, 63 49-61, 65 429-  
 442, 66 391-415, 68 791-793, 69 319-333, 1029-  
 1036, 70 228-265, 743-747, 748-754, 71 316-317,  
 72 851-855, 74 572-580, (Supplement, August  
 100-108), 75 659-666, 76 1100-1105, 1106-1109,  
 77 539-542, 80 431-433  
 McDougall, J B, 64 218-222  
 McDowell, CHISHOLM, 69 612-617  
 McDowell, MARION, 62 29-44  
 McElroy, ROBERT J, 69 604-611  
 McGETTIGAN, MARIE T, 70 71-90  
 McGREGOR, MAURICE, 77 209-220, 78 692-696  
 MACIAS, JOSÉ DE J, 79 265-272  
 MacINTYRE, SYLVIA B, 80 915-918  
 MACK, IRVING, 64 50-63

- MACKANESS, G B , 66 125-133, 67 322-340, 69 479-194, 495-504, 690-704, 74 718-728  
 McKEE, A P , 72 687-689  
 McKEE, CLARA M , 60 90-108, 109-120, 121-130, 63 556-567  
 McKENNAIS, HERBERT, JR , 73 956-959  
 McKENZIE, DORIS, 65 511-518  
 MACKEPFRANG, BENT, 76 914-915  
 McKIM, ANSON, 66 457-476  
 McKINNEY, RUTH A , 77 1019-1022  
 McKNIGHT, HERBERT V , 70 701-703  
 McKUSICK, VICTOR A , 72 12-34  
 McLAREN, LEROY C , 71 260-265, 266-271  
 MacLEAN, K S , 71 302-304  
 McLEAN, KENNETH H , 80(Supplement, July 58-64)  
 McLEAN, ROSS, L , 75 420-431, 514-516  
 McLELLAN, FRED C , 69 618-624  
 MacLEOD, H M , 68 400-410  
 McMILLEN, SHIRLEY, 76 103-107, 108-122, 80 434-437  
 MacNAMARA, J , 70 274-284  
 McPHEE, HARRY R , 61 138-144  
 MacQUIGG, RODGER E , 72 465-478  
 MacRAE, D M , 61 355-368  
 McROBERTS, CARRIE C , 71 762-764  
 MAGNUS, KNUT, 72 126-128, 74 297-303  
 MAGNUSSON, MOGFNS, 72 126-128, 74 297-303  
 MAHADY, STEPHEN C F , 68 238-248, 72 242-244, 73 776-778  
 MAHER, JOHN R , 75 517-518, 999-1002, 76 852-861, 77 501-505  
 MAHEUX, P , 71 867-876  
 MAHON, HUGH W , 61 543-555  
 MAIDEN, SYDNER D , 62 549-554  
 MAIER, HERBERT C , 63 220-226, 65 206-209  
 MAILLARD, EDGAR R , 64 675-681, 66 762-764  
 MAIS, EDWARD L , 79 307-314  
 MAISEL, BERNARD, 78 623-631  
 MAJOR, JAMES W , 61 346-352  
 MAJUMDAR, NIRMAL K , 75 644-647  
 MALIN, RUTH B , 60 439-447, 448-454  
 MALKIEL, SAUL, 68 629-630  
 MALLMANN, W L , 71 382-389  
 MALONE, LUKE, 65 511-518  
 MANDEL, W , 74 796-797  
 MANDELBAUM, THEODORE, 66 594-600  
 MANKIEWICZ, EDITH, 75 836-840  
 MANTEN, A , 74 633-637, 958-960  
 MANTZ, HERBERT L , 69 227-233, 234-240  
 MARCHE, J , 79 6-18  
 MARCHESI, VINCENT, 66 699-721  
 MARCUS, STANLEY, 75 849-850, 77 983-989, 80 264-266  
 MARDIS, RICHARD E , 63 295-311  
 MARESH, F , 59 391-401  
 MARGOLIS, JACK, 75 828-832  
 MARIETTE, E S , 59 113-127  
 MARION, ARTHUR J , 80 59-64  
 MARK, DONALD D , 79 440-449  
 MARK, HARRIS J , 68 286-289, 73 593-596  
 MARKAROGLU, L , 66 100-103  
 MARKS, ASHER, 74 317-342  
 MARKS, J , 71 566-572  
 MARKS, ROBERT H , 78 871-883  
 MARMION, THOMAS, 80 278  
 MAROLLA, MICHAEL M , 71 295-298  
 MARRANGONI, ALBERT G , 72 257-267  
 MARSH, K , 71 302-304  
 MARSHAK, ALFRED, 62 333, 65 75-82  
 MARSHALL, EDWARD E , 63 103-118  
 MARTIN, C J , 73 330-337, 77 260-270  
 MARTIN, FRANK E , 66 509-521  
 MARTIN, G E , 66 501  
 MARTIN, JOSEPHINE D , 66 63-76  
 MARTINEAU, PERRY C , 66 151-160  
 MASCHER, WILLI, 63 501-525, 64 469-470  
 MASON, CARL B , 80 6-11  
 MASON, DANIEL, 69 657-672  
 MASON, RICHARD C , 74 972-976  
 MASON, W ROY, 66 345-350  
 MATHEWSON, JOHN A , 74 142-144  
 MATHISEN, ARNE K , 65 443-450  
 MATSUNAGA, KIYOTERU, 77 482-491, 80 240-248, 535-542  
 MATTERN, C F T , 65 48-63  
 MATTHIESEN, DON E , 69 829-836  
 MATTILL, P M , 59 113-127  
 MATTINSON, MARJORIE W , 65 572-588, 69 92-103  
 MATTSON, S -B , 78 536-546  
 MAUDERLI, WALTER, 77 375-386  
 MAUSER, MARIE, 80 274-276  
 MAIER, EDGAR, 62(Supplement, July 80-89)  
 MAIER, EDMUND, 69 419-442  
 MAYER, R L , 70 121-129, 130-138, 77 694-702, 703-711  
 MAYER, S W , 71 889-891  
 MATOCK, ROBERT L , 71 529-543  
 MEADE, GORDON M , 59 429-437, 60 541-546, 65 754-758  
 MEADE, RICHARD H , JR , 60 683-698  
 MEADOR, ROBERT S , 74 638-640, 75 53-61, 76 47-63  
 MEADOW, PAULINE M , 73 726-734  
 MEANS, J A , 63 1-3  
 MEDLAR, EDGAR M , 62 101-108, 63 449-458, 66 381-382, 71(Supplement, March 1-244)  
 MEIER, PAUL, 62 190-208, 65 201-205, (Supplement, January 1-50)  
 MEIER, WALTER A , 69 543-553  
 MEINDERSMA, MARYLIN S , 80 915-918  
 MEISSNER, WILLIAM A , 60 406-418  
 MELANIDES, G , 72 859-862  
 MELICK, D W , 62 116-117, 77 17-21  
 MELLETTE, SUSAN J , 69 824-828  
 MELVIN, IRENE, 63 459-469, 78 83-92, 799-801

- MENDENHALL, JOHN T, 72 569-576  
 MERRILL, RICHARD S, 77 177-180, 712-715  
 MERRILL, DUANE L, 77 561-592  
 MERTENS, ANTON, 61 20-38  
 MEYER, ANDREW H, 66 512-517  
 MLYER, B W, 73 690-703  
 MEYER, JOHANNIS, 70 102-112  
 MEYER, K F, 71 560-571  
 MEYER, MARINTHE, 71 765-766  
 MIERS, CHARLES L, 71 371-381  
 MYERS, HARVEY I, 71 590-596  
 MICHAEL, MAX, 62 103-107  
 MICK, FRANK, 64 153-160  
 MIDDLEBROOK, GARDNER, 62 223-226, 65 765-767,  
 69 471-472, 70 165-175, 501-508, 641-661, 922,  
 1030-1011, 1102-1103, 71 390-405, 111-146,  
 765-766, 72 653-658, 693, 73 911-955, 74 42-49,  
 75 155-156, 650-658, 80 1-5, 587-589  
 MIDDLETOWN, JOHN W, 62 139-140  
 MIETZSCH, FRITZ, 61 1-7  
 MIHALY, JOHN P, 69 673-681, 79 307-311  
 MIKI, KATSUJI, 77 482-491, 80 210-218, 535-542  
 MIKOL, EDWARD X, 66 16-27  
 MILGRAM, LILLIAN, 75 897-911  
 MILLER, BENJAMIN F, 63 192  
 MILLER, D V, 71 178-187  
 MILLER, DONALD B, 77 818-857, 80 825-832  
 MILLER, DOROTHY E, 60 189-205  
 MILLER, EARL R, 64 225-218, 249-255  
 MILLER, ELIZABETH E, 73 547-562  
 MILLER, FRANK L, 66 534-511, 69 58-64  
 MILLER, IRVING L, 73 716-725  
 MILLER, JAMES N, 68 31-41  
 MILLER, JOSEPH B, 62 91-98  
 MILLER, JOSEPH M, 60 212-222  
 MILLER, RUSSELL, JR, 70 1053-1063  
 MILLER, TRACY B, 75 999-1002  
 MILLER, WALTER T, 77 260-270  
 MILLER, WILLIAM F, 71 693-703, 79 315-322  
 MILLER, WILLIAM M, 74 638-640  
 MILLS, CRYSTAL C, 75 420-431  
 MILLS, LEWIS C, 68 541-547  
 MILLS, WALDO H, 71 280-290  
 MINARD, EUGENE W, 73 882-891  
 MINKIN, ALBERT, 70 728-733  
 MINOR, GEORGE R, 73 79-98  
 MISCALL, LAURENCE, 73 831-852  
 MISENER, F J, 79 468-473  
 MITCHELL, MILDRED B, 79 533-536  
 MITCHELL, ROGER S, 60 168-182, 183-188, 61 809-  
 825, 64 1-20, 21-26, 27-40, 227-140, 141-150,  
 151-158, 67 401-420, 421-431, 68 863-873,  
 69 963-967, 71 602-603, 72 487-501, 502-512,  
 653-658, 75 180-298, 346-347, 76 152-158, 491-  
 496, 508-509, 80 108-110, 207-215, (Supple-  
 ment, July 2-4, 213)  
 MITCHISON, D A, 69 640-644, 74 (Supplement,  
 August 109-116)  
 MIURA, KOJI, 76 298-300  
 MIZUNO, DENJI, 75 488-491  
 MIZUTANI, R H, 77 703-711  
 MOEY, CHESTER W, 60 1-14  
 MOLD, JAMES D, 63 1-6  
 MOLLOY, MOLLIF, 63 487-489, 65 191-200  
 MOINAR, LADISLAW, 66 90-91  
 MOLOMUT, NORMAN, 62 337-344, 67 101-102  
 MOLTHAN, LINDALL, 71 220-227  
 MONROE, JAMES, 62 572-581, 71 193-200, 73 776-  
 778, 77 413-417  
 MONTALBINE, VINCENT, 76 643-659, 78 451-461,  
 570-575, 79 66-71  
 MONTES, MANO, 75 343-344, 79 362-370  
 MOORE, FREDERICK J, 75 618-623, 621-629, 76 752-  
 760, 80 216-222  
 MOORE, JANE, 78 576-582  
 MOORE, T, 80 223-231  
 MOORMAN, LEWIS J, 61 586-591, 62 446-448  
 MORALES, SOLEDAD M, 75 594-600  
 MORAVIC, MARGARET, 63 679-693  
 MORGAN, RUSSELL H, 64 313-317  
 MORGANTE, O, 76 832-851  
 MORGENSTERN, PHILIP, 59 53-67, 60 25-31  
 MORRIS, CHARLES S, 78 274-281, 524-535, 79 512-  
 517, 577-590  
 MORRIS, GWYNETH L, 68 794-795  
 MORRISSEY, JOHN F, 80 855-865  
 MORSE, DRIVEN P, 75 865-884  
 MORSE, W C, 69 464-468, 72 840-842  
 MORTON, DAVID E, 73 351-361  
 MORTON, J W, 79 474-483  
 MORTON, M E, 71 889-891  
 MOSELEY, CHARLES H, 59 481-493  
 MOSER, KENNETH M, 76 480-490  
 MOSHIN, JEAN R, 68 31-41, 594-602, 70 344-348  
 MOTAMED, GHASSEM, 80 587-589  
 MOTIWALE, ACHYUT G, 77 168-171  
 MOTLEY, HURLEY L, 59 270-288, 61 201-225,  
 76 601-615, 77 737-748  
 MOULON, MARIO, 73 61-71  
 MOUNT, FRANK W, 66 632-635, 67 108-113, 539-  
 543, 68 264-269, 70 521-526, 80 371-387  
 MOUSA, A H, 79 119-133  
 MOYER, JOHN H, 61 131-137, 299-322, 63 176-193,  
 255-274, 399-416, 64 659-668, 68 541-547  
 MOYER, RALPH E, 61 875-880, 62 563-571, 64 41-  
 49, 70 413-422, 924, 76 1097-1099, 79 90-93  
 MUCHMORE, HAROLD G, 80 267-268  
 MUDD, STUART, 67 59-73, 68 625-628  
 MUELLER, EDWIN E, 59 391-401, 60 794-800,  
 67 292-298, 70 518-520, 533-534, 71 766  
 MUELLER, EUGENE, 80 (Supplement, July 194-  
 202)  
 MUENDEL, HAROLD J, 67 232-246  
 MULLIN, EDWARD W, 67 652-656  
 MULVHILL, D A, 66 605-614  
 MUNROE, W G C, 65 523-546

MURPHY, JAMES D , 63 81-84, 66 436-448, 67 22-28,  
68 535-540, 71 892-893, 73 191-218  
MURPHY, MARION E , 72 690-692  
MURRAY, FRANCIS J , 80 371-387  
MUSCHENHEIM, CARL, 60 140-142, 63 49-61, 65 429-  
442, 66 391-415, 68 791-793, 796-798, 69 319-  
333, 843-851, 70 228-265, 743-747, 71 316-317,  
72 1-11, 851-855, 75 659-666, 77 539-542,  
80 431-433  
MUSSER, MARC J , 66 449-456  
MYERS, J ARTHUR, 71 885-888, 73 620-636, 75 442-  
460, 79 19-30, 80 100-107  
MYRVIK, QUENTIN N , 64 669-674, 67 217-231,  
68 564-574, 69 406-418, 73 589-592, 78 93-100,  
79 339-343

## N

NACMAN, MARTIN, 80 111-112  
NAEGELE, CHARLES F , 64 564-571  
NAGAH, A M EL, 79 119-133  
NAHAS, HECTOR C , 64 620-629  
NAIR, K G S , 75 553-575  
NAKAJIMA, MICHIO, 78 884-898  
NAKAMURA, SHIGERU, 75 99-104  
NAKANO, AKINORI, 79 232-237  
NARITA, MITSUNORI, 69 297-299  
NATHAN, ARTHUR, 80 424-425  
NATIONAL TUBERCULOSIS ASSOCIATION—VETER-  
ANS ADMINISTRATION, 72 866-868  
NAYER, H R , 62 654-666, 67 509-513  
NAYLOR-FOOTE, A W C , 79 374-377  
NÈGRE, L , 68 467-470, 74 807-808  
NEIMAN, IRWIN S , 59 102-105  
NELSON, CLARENCE, 60 45-50  
NELSON, SOL S , 68 127-135  
NELSON, WALDO E , 74 (Supplement, August 256-  
266)  
NEMEC, F C , 59 113-127  
NEMIR, ROSA LEE, 62 618-631, 66 63-76  
NEPTUNE, WILFORD B , 61 185-192, 63 710-713,  
64 394-407  
NETSKY, MARTIN G , 62 586-593  
NETZER, SOLOMON, 63 62-66  
NEUMANN, GERTRUDE, 77 245-259  
NEVILL, JOHN F , JR , 73 134-138  
NEWELL, R R , 69 556-584  
NEWMAN, LOUIS B , 71 272-279  
NEWMAN, MELVIN M , 71 676-692, 80 806-824  
NEWMAN, ROBERT W , 79 204-211  
NEWTON, J K , 63 476-479  
NICHOLS, GEORGE P , 76 1016-1030  
NICHOLS, NORMAN J , 80 833-844, 895-901  
NICKERSON, GRANVILLE H , 76 832-851, 78 485  
NIMITZ, HERMAN J 70 430-441  
NINOS, GEORGE S , 73 434-437  
NISSEN MEYER, SVEN, 66 292-313, 69 383-395  
NODA, YO, 78 121-126, 79 371-373

NOLAN, RICHARD B , 73 831-852  
NOLL, HANS, 67 828-852  
NORMAN, JAMES O , 71 762-764  
NORMAN, JANE W , 65 692-708  
NORVITT, LEMBIT, 67 258-260  
NOUFFLARD, HENRIETTE, 72 330-339, 80 326-339  
NOZZOLI, FRANCO, 66 90-94  
NUGENT, C A , 78 682-691  
NUKADA, SUSM, 74 478  
NUNGESTER, W J , 62 418-427, 63 372-380, 65 477-  
480  
NUTTER, J E , 79 339-343  
NYKA, WALENTY, 73 251-265, 75 420-431

## O

OATWAY, WILLIAM H , JR , 63 490-492, 80 108  
O'BRIEN, BRENDAN, 73 219-228, 77 952-967  
O'BRIEN, E J , 59 30-38  
O'BRIEN, WILLIAM B , 68 874-884  
OCHS, JACOB, 66 750-757  
OCHSNER, ALTON, 70 763-783  
OCHSNER, SEYMOUR, 77 496-500  
O'CONNELL, HUGH V , 78 21-37  
O'CONNOR, JOHN B , 59 402-414, 60 264-268,  
63 312-324, 68 270-272  
ODA, U , 70 465-475, 641-664  
ODERR, CHARLES P , 80 (Supplement, July 104-  
112)  
OECHSLI, FRANK W , 74 590-596  
OESTREICHER, ROLF, 70 504-508, 71 390-405,  
72 693  
OGAWA, G , 71 465-472  
OGAWA, YASAKA, 75 99-104  
OGINSKY, EVELYN L , 74 78-83  
OHLSON, MARGARET A , 60 455-465  
OHR, IRVING, 72 653-658  
OHTA, SHIGEO, 79 329-338  
OKANO, TAKESHI, 68 535-540  
OKAWAKI, MABEL S , 77 536-538  
O'LEARY, BETTY, 64 71-76  
O'LEARY, DENIS J , 73 501-518  
OLINGER, JOHN K , 65 88-92  
OLIVEIRA-LIMA, A , 78 346-352  
OLIVER, ROBERT K , 71 291-294  
OLSEN, ARTHUR M , 60 32-38, 74 454-456  
OLSON, BYRON J , 62 403-407, 65 48-63  
OLSON, DONALD E , 66 449-456, 68 657-677,  
70 102-108  
OLSON, EDWARD C , 75 584-587  
OLSON, HOWARD D , 75 675-677  
O'NEILL, E F , 72 577-600  
ORESKEs, IRWIN, 67 299-321, 70 334-343  
ORGANICK, AVRUM, 72 851-855, 79 799-804  
ORINIUS, ERIK, 78 363-375, 376-390, 79 450-456  
ORITT, JACOB E , 69 1045-1050  
ORMOND, LOUISE, 69 319-333, 70 228-265, 743-747  
ORNSTEIN, GEORGE G , 67 212-216



O'ROURKE, PAUL V, 59 30-38  
 ORTON, S P, 80 388-397  
 OSATO, SHUNGO, 71 258-276  
 OSHIMA, SHUNSAKU, 76 90-109, 77 524-528, 529-535, 78 884-898  
 OSTROM, C A, 79 511  
 OSWALD, NEVILLE, 75 340-342  
 OTT, ROY H, JR, 65 692-708  
 OTTOSEN, POUL, 62 434-438  
 OUSLEY, JOSEPH L, 68 523-534  
 OLFERHOLT, RICHARD H, 60 406-418, 62 491-500, 75 865-884  
 OWEN, CORA RUST, 61 705-718, 66 58-62  
 OWEN, GEORGE C, 61 474-482, 66 261-270, 67 267  
 OWENS, RUTH P, 76 899-901  
 OYAMA, TSUTOMU, 72 613-632, 73 472-484  
 OZOLS, J, 75 1007-1008, 76 159-160

## P

PACHTER, MAURICE, 68 796-798  
 PACKALÉN, THOROLF, 69 205-211, 80 19-25, 410-414  
 PACKARD, EDWARD N, 62 (Supplement, July 1-2), 69 50-57  
 PACKARD, JOHN S, 63 706-709  
 PADIATELLIS, C, 72 527-536  
 PAGEL, WALTER, 59 311-316, 65 673-691  
 PAHNELAS, ELIZABETH V, 73 956-959  
 PAINE, A L, 63 644-656, 78 411-425  
 PALACIOS, HECTOR, 68 760-770  
 PALCHANIS, WM T, 65 451-454  
 PALDINO, RITA L, 80 398-403  
 PALEN, M IMOGENE, 75 148-152  
 PALEY, SAMUEL S, 79 307-314  
 PALITZ, LEO S, 75 461-468, 77 232-244  
 PALMER, CARROLL E, 68 462-466, 68 678-694, 69 383-395, 73 1-18, 74 917-939, 76 517-539, 77 546-550, 877-907, 80 747-749  
 PALMER, EDDY D, 61 116-130  
 PAMPLONA, P A, 60 501-513  
 P'AN, S Y, 63 1-3, 44-48, 66 100-103  
 PANDE, A, 70 328-333  
 PANGBORN, MARI C, 66 335-344, 69 300-303  
 PANISSET, MAURICE, 71 319-321  
 PANSY, FELIX, 60 121-130, 65 761-764, 67 354-365, 366-375, 68 284-285  
 PANTAZIS, S, 72 859-862  
 PAOLETTI, R, 80 110-111  
 PAPPAGIANIS, DEMOSTHENES, 74 147-148  
 PAPPENHEIMER, A M, 71 88-96, 97-111  
 PAREJA CORONEL, ARMANDO, 75 987-991  
 PARKER, F, JR, 70 130-138  
 PARKER, JUNE, 62 58-66  
 PARKER, MALCOLM V, 72 119-122  
 PARKER, ROBERT F, 76 899-901  
 PARLETT, ROBERT C, 73 637-649, 77 450-461, 462-472, 80 153-166, 886-894  
 PARROTT, D K, 74 810

PARSONS, ROBERT J, 66 542-547  
 PATERSON, A B, 69 806-817  
 PATIALA, JORNA, 70 153-464  
 PATNODE, ROBERT A, 60 628-633, 62 484-490, 66 99, 69 599-603, 710-723, 72 117-118, 340-344, 685-686, 856-858, 73 246-250, 75 83-92, 630-637, 78 138-139, 79 323-328, 382-383  
 PATTERSON, R A, 74 284-288  
 PATTON, ELIZABETH A, 65 1-23  
 PATTON, WILLIAM E, 67 755-778, 779-797  
 PAUL, W, 74 511-532  
 PAULEEN, M M, 70 483-489, 76 232-246  
 PAULSON, DONALD L, 64 477-488, 76 970-982  
 PAVLATOU, M, 72 859-862  
 PAWLOWSKI, JOSEPH M, 76 988-1001  
 PAINE, HOWARD M, 60 332-342, 66 548-566, 68 103-118, 70 701-703  
 PAYSEUR, COYT R, 78 906-915  
 PEABODY, J WINTHROP, 68 775-781, 74 106-111  
 PEARSON, RAYMOND, 62 29-44  
 PEARSON, ROY T, 66 509-521, 68 177-187  
 PEASLEY, E D, 76 669-670  
 PECK, MORDANT E, 65 339-343  
 PECK, W M, 61 387-398  
 PECORA, DAVID V, 65 83-87, 73 586-588, 75 781-792, 77 83-92, 79 41-46, 134-141, 679  
 PEEPLES, WILLIAM J, 69 111-115  
 PEER, EDGAR T, 75 153-155  
 PEIZER, LENORE R, 67 598-603, 68 290-291, 734-738, 69 26-36, 1022-1028, 70 349-359, 363-366, 728-733, 71 305-307, 841-859, 72 143-150, 246-251, 74 293-296, 428-437, 76 732-751, 78 788-792  
 PEKICH, A M, 63 44-48  
 PENIDO, R F, 70 109-120  
 PENNER, MILDRED A, 63 4-6, 7-16  
 PENSO, ANGEL DELEON, 68 760-770  
 PEPTS, J, 71 49-73, 80 167-180  
 PÉREZ-TAMAYO, RUI, 77 473-481, 79 246-250, 80 554-558  
 PERKINS, EVAN K, 66 77-85  
 PERKINS, JAMES E, 66 615-618, 77 155-161, 78 810, 80 (Supplement, October 138-139)  
 PERKINS, REV B, 75 145-147, 76 906-908  
 PERKINS, ROBERT B, 64 659-668  
 PERMUTT, SOLBERT, 77 245-259  
 PERR, HERBERT M, 63 597-602  
 PERRY, C R, 72 840-842  
 PERRY, THOMAS L, 65 325-331  
 PETERSDORF, ROBERT G, 79 238-243  
 PETERSON, AGNES, 78 871-883  
 PETTER, JOHN B, 72 453-464  
 PETTY, T, 80 (Supplement, July 147-151)  
 PFEIFFER SCHEFF, IRENE M, 62 374-389  
 PFEIFFER, EHRENFRIED E, 76 867-870  
 PFUETZE, KARI H, 63 427-433, 68 912-925, 71 752-754, 78 649-650  
 PHILLIPS, CHARLES, 79 362-370

- PHILLIPS, SAMUEL, 60 618-653, 62 549-554, 63 116-118, 69 113-150, 70 176-182, 72 667-671, 843-845, 73 701-715, 75 667-669, 78 135-137, 79 273-283, 80 611-617, 721-731, 909-910  
 PHILPOT, F J, 66 28-35  
 PIAGGIO, ARISTO A, 66 1-15  
 PICARD, D, 77 839-847  
 PICCAGHI, RUTH W, 60 557-563  
 PICKETT, WILLIAM H, 62 439-440  
 PIERCE, CYNTHIA H, 74 655-666, 667-682, 683-698, 699-717, 75 331-337, 359-409, 692-693  
 PIERCE, JOHN A, 80 (Supplement, July 15-48)  
 PIERSON, BARBARA J, 68 18-64  
 PIERSON, CHARLES E, 73 123-127  
 PIETRASZYK, CASIMIR F, 70 672-688  
 PIETHROWSKI, JOSEPH J, 70 123-429  
 PIKULA, MARIA, 67 808-827  
 PILCHER, HELEN, 62 58-66  
 PILLSBURY, DONALD M, 63 141-148  
 PILPEL, MICHAEL, 68 782-785  
 PINES, A, 79 818  
 PINNER, MAX, 59 449-460  
 PINNEY, CHARLES T, 74 111-444, 77 32-38  
 PITAL, ABRAHAM, 78 111-116  
 PITAL, RUTH C, 78 111-116  
 PITNER, GEORGIA, 63 679-693  
 PITTS, FORREST W, 61 862-867, 62 610-617  
 PIZZALATO, PHILIP, 80 (Supplement, July 104-112)  
 PLACE, RONALD, 60 706-714  
 PLATOU, R V, 74 (Supplement, August 160-168)  
 PLATT, WARREN D, 6 514-519  
 PLESSINGER, VIRGIL A, 60 589-603  
 PLUCKETT, ROBERT E, 61 51-56  
 POET, RAYMOND B, 65 484-485  
 POINDEXTER, HILDRUS A, 67 665-668  
 POLACHEK, ABRAHAM A, 61 868-874  
 POLACK, ROBERT T, 64 307-312  
 POLAYES, SILIK H, 75 326-330  
 POLLAK, ANN, 71 74-87, 73 917-929  
 POLLAK, MAXIM, 72 107-116  
 PONGOR, FERENC, 79 652-658  
 POOLE, GRAHAM, 73 805-817  
 POPE, HILDA (*see also* WILLETT, HILDA POPE), 62 34-47, 68 928-939, 69 705-709, 73 735-747  
 POPPE DE FIGUEIREDO, FLAVIO, 71 186-192  
 POPPER, HANS, 75 295-302, 77 120-133, 80 71-77  
 PORTELANCE, VINCENT, 79 296-306  
 POTTEANGER, F M, 60 639-647, 68 933-937  
 POTTER, EDITH L, 80 (Supplement, July 5-20)  
 POTTS, WILLIAM L, 64 394-407  
 POWELL, MARY E, 63 717  
 PRATT, PHILIP C, 59 664-673, 674-678, 62 455-474, 64 87-101, 66 194-212, 67 29-44, 69 766-789, 841-842, 70 714-727, 74 874-884, 75 93-98, 76 880-887, 77 62-72, 78 839-847  
 PREHEIM, DELBERT V, 65 339-343  
 PREMINGER, MAX, 66 86-89  
 PREUSS, FRED, 70 285-295, 76 123-131  
 PRICE, ROBERT A, 77 729-736  
 PRICE, ZANE, 76 964-969  
 PRIETO, L C, 75 259-265  
 PRINCI, FRANK, 60 706-714  
 PRIOR, JOHN A, 63 538-546, 66 588-593  
 PRITCHARD, ELIZABETH, 75 1003-1006  
 PROUDFIT, WILLIAM L, 75 469-475  
 PROUT, CURTIS T, 65 481-483  
 PRIOR, W W, 74 309-316  
 PUBLIC HEALTH SERVICE *See* U S PUBLIC HEALTH SERVICE  
 PLUCKETT, THOMAS F, 67 453-476, 70 320-327  
 PUFFER, RUTH R, 65 111-127  
 PUZIK, V I, 79 497-501  
 PYLE, MARJORIE M, 81 752-754, 78 649-650
- Q**  
 QUARLES, CONSTANCE, 70 701-713  
 QUINLAN, J J, 61 355-368, 79 468-473
- R**  
 RACK, FRANK J, 63 227-229  
 RADNER, DAVID B, 65 93-99  
 RAFFEL, SIDNEY, 74 (Supplement, August 60-74), 80 849-854  
 RAHN, HERMANN, 76 1063-1070  
 RAINE, FORRESTER, 61 474-482  
 RAKE, GEOFFREY, 60 90-108, 109-120, 121-130, 140-142, 63 556-567  
 RAKOWER, JOSEPH, 67 85-93  
 RALEIGH, JAMES W, 69 963-967, 73 123-127, 266-275, 75 538-552, 76 540-558  
 RAMSAY, J H ROLLAND, 79 818  
 RAMSEY, HAL H, 80 267-268  
 RANDALL, HARRISON M, 63 372-380, 65 477-480, 69 505-510, 73 529-538, 75 843-845  
 RANKIN, JOHN, 74 29-41  
 RANNEY, ALBERT F, 77 908-922  
 RANTZ, LOWELL A, 64 318-321  
 RAPPAPORT, ISRAEL, 62 (Supplement, July 80-89)  
 RASMUSSEN, HOWARD K, 72 569-576, 75 745-755  
 RAUCHWERGER, SOLOMON M, 59 128-139  
 RAUF, ROBERT A, 80 806-824  
 RAY, C JACK, 70 763-783  
 RAY, EDWARD S, 65 627-630  
 RAY, HOMER, 74 830-834  
 RAYL, JOHN E, 73 191-218  
 READ, JOHN, 78 353-367  
 REAM, CHARLES R, 72 381-385  
 REAMES, H R, 75 588-593  
 REBUCK, JOHN W, 69 216-226  
 REDEMANN, C T, 62 475-480  
 REDING, FRANKLIN S, 73 690-703  
 REDLICH-MOSHIN, JEAN, 70 344-348  
 REDMOND, W B, 73 907-916, 80 232-239  
 REDNER, WALLACE J, JR, 67 859-868

- REIJTSMA, KRITH, 71 351-357  
 REES, R J W, 76 915-916  
 REES, ROBERTS M, 69 513-553  
 REEVES, FREDRIC C, 63 119-158  
 REIFERS, J T, 80 (Supplement, July 128)  
 REGAN, FREDRIC D, 61 561-571  
 REGLI, J, 79 351-356  
 REGNA, P P, 60 808-810, 63 1-3  
 REHR, CAROLINE, 77 462-472  
 REHR, CAROLIN A, 80 886-891  
 REIDT, WILLIAM U, 76 33-46  
 REILLY, J C, 63 41-48, 66 100-103  
 REIMANN, ARTHUR F, 71 121-127  
 REINMUTH, OSCAR M, 64 508-515  
 REISER, HOWARD G, 61 323-334  
 REISNER, DAVID, 66 666-679, 71 841-859  
 REISS, JACK, 76 315-319  
 RENZETTI, ATTILIO D, JR, 61 583-601, 74 128-135, 75 638-643, 78 101-202, 79 72-77  
 REPPA, J J, 63 587-590  
 RESNICK, ALBERT, 62 128-143  
 REUBER, MELVIN D, 72 675-684  
 REYNOLDS, LESTER T, 60 773-787  
 RHEINS, MELVIN S, 72 210-217, 73 563-570, 571-575, 74 229-238, 239-241, 756-763, 764-772, 75 958-964, 78 259-267, 79 622-630, 631-640  
 RHULAND, L E, 75 588-593, 77 976-982  
 RICHARDSON JONES, A, 68 739-745  
 RICHARDSON, RUSSELL, 65 (Supplement, January 1-50)  
 RICHBURG, PAUL L, 71 693-703, 76 47-63  
 RICHERT, JOEL H, 80 760  
 RICHMOND, LEA, 62 632-637  
 RIDDELL, R W, 70 442-452, 80 167-180  
 RIEBER, CHARLES W, 63 213-219, 64 448-452  
 RIEMENSNIJDER, DICK K, 75 675-677, 992-994, 995-998, 76 152-158, 683-691, 80 108-110  
 RIGDON, R H, 61 247-256  
 RIGGINS, H McLEOD, 59 140-147, 62 572-581, 67 74-84  
 RIGGS, HELENA E, 74 830-834  
 RIGLER, LEO, 69 566-584  
 RIKLI, ARTHUR E, 79 427-439  
 RILEY, EDGAR ALSOP, 62 231-285, 67 613-628, 71 584-591, 80 426-430  
 RILEY, RICHARD L, 71 249-259, 75 420-431, 76 931-941  
 RIST, NOËL, 74 (Supplement, August 75-89), 79 1-5, 6-18  
 RITTENBERG, DAVID, 71 609-616  
 RITTER, NATHANIEL S, 62 586-593  
 RIVOIRE, ZINA C, 67 808-827  
 ROBB, C J, 80 110  
 ROBBINS, S L, 70 130-138  
 ROBERTS, ALBERT, 80 582-584  
 ROBERTS, E GWYN, 60 634-638, 61 563-568  
 ROBERTS, GWYN, 64 557-563  
 ROBERTS, ROBERT W, 80 904-908  
 ROBERTSON, DOUGLAS H, 69 618-621  
 ROBINS, ARTHUR B, 69 26-36, 1057-1058, 70 1042-1053, 72 143-150, 74 293-296, 480, 75 41-52, 77 359-363, 78 725-731  
 ROBINSON, ARTHUR, 71 765-766  
 ROBINSON, FRANCES, 69 1016-1021, 1051-1053, 76 703-705  
 ROBINSON, G CANBY, 63 365-371  
 ROBINSON, HARRY J, 68 212-219, 70 423-429, 74 972-976  
 ROBINSON, JERRYDEAN H, 62 484-490  
 ROBINSON, JOE S, 77 73-82  
 ROBINSON, JOSEPH L, 73 690-703  
 ROBITZKE, EDWARD H, 65 402-428, 67 212-216  
 ROBSON, J M, 71 1-6, 75 756-767, 78 203-225, 80 871-875  
 ROCHF, A D, 77 839-847  
 ROCHF, PAT, JR, 65 603-611  
 ROCKFLY, E E, 78 815-821, 79 773-779  
 RODRÍGUEZ PASTOR, J, 67 132-153, 70 1099-1101  
 ROE, M D, 65 376-391  
 ROESSLER, WILLIAM G, 73 716-725  
 ROGERS, A E T, 61 643-647, 70 285-295  
 ROGERS, BETTY S, 76 568-578  
 ROGERS, DAVID E, 69 1029-1036, 71 371-381  
 ROGERS, WILLIAM K, 74 188-195  
 ROGERS, WILLIAM L, 71 30-48, 77 418-422  
 ROGUL, MARVIN, 76 697-702  
 ROLL, LEWIS R, 69 84-91  
 ROMÁN, LIVIRA, 77 146-154  
 ROMANSKY, MONROE J, 80 590-593  
 ROORBACH, ELIZABETH H, 72 465-478  
 ROPER, WILLIAM H, 61 678-689, 725-729, 71 616-634, 72 242-244, 75 1-40  
 RORABAUGH, MILDRED E, 67 432-439  
 ROSCH, PAUL J, 70 841-851  
 ROSE, HAROLD D, 80 249-254  
 ROSE, ISADORE, 65 332-338  
 ROSE, N R, 78 637-643  
 ROSENBLATT, GEORGE, 76 909-911  
 ROSENTHAL, IRA M, 62 441-445  
 ROSENTHAL, SOL ROY, 60 236-248, 61 95-105, 106-115, 730-734, 64 698-701, 65 344-346, 641, 77 778-788, 79 105  
 ROSENZWEIG, ABRAHAM L, 70 176-177  
 ROSNER, BEN, 70 285-295  
 ROSS, JOSEPH, 62 109-111, 63 67-75  
 ROSS, S GRAHAM, 76 832-851  
 ROTH, LLOYD J, 75 71-82  
 ROTHSTEIN, EMIL, 59 39-49, 50-52, 64 686-690, 66 233-239, 381, 69 65-70, 287-296, 980-990, 70 509-517  
 ROUCH, L C, 78 251-258  
 ROULET, F, 68 771-774  
 ROUTIEN, J B, 63 1-3  
 ROWE, CHARLOTTE, 63 667-671, 66 621-622  
 ROYE, W E, 70 373-377

- RUBBO, SIDNEY D , 68 48-61, 76 331-345, 346-359, 78 251-258, 79 492-496  
 RUBINMAN, WILLIAM, 76 761-769  
 RUBIN, BERNARD, 65 392-401, 67 644-651  
 RUBIN, MORRIS, 60 273-287  
 RUBIN, RUTH C , 80 855-865  
 RUMML, DAVID, 76 140-143  
 RUNYON, ERNEST H , 70 374, 79 663-665, 80 277-278  
 RUPP, CHARLES, 71 830-834  
 RUSSE, HENRY P , 72 236-241, 713-717  
 RUSSELL, KEITH P , 63 603-607  
 RUSSALI, M , 62 638-644  
 RUSSPII, MORTIMER, 68 796-798  
 RUSSFELI, WILLIAM F , JR , 66 619-620, 70 1030-1041, 71 390-405, 411-416, 73 911-955, 74 (Supplement, August 267-277), 796-797, 79 666-668, 80 587-588  
 RYAN, THOMAS C , 61 426-430  
 RZUCIDLO, LUDWIK T , 77 1026-1029
- S**
- SADUSEK, JOSEPH F , JR , 59 402-414  
 SAGAWA, I , 71 465-472  
 SAGE, WILLIAM H , III, 72 663-666, 74 622-623  
 SAHN, STANLEY H , 62 219-222  
 SAJA, JOSEPH J , 68 799-802  
 SAIFER, ABRAHAM, 67 299-321, 70 331-343, 74 15-28  
 ST-PIERRE, JACQUES, 79 296-306  
 ST RAYMOND, ALBERT H , JR , 71 295-298  
 SAKAGUCHI, SANBO, 62 645-653  
 SALINE, MIRON, 64 448-452  
 SALKIN, DAVID, 63 721-722, 71 361-370, 74 376-387, 77 181-183, 80 59-64, 447-449  
 SALOMON, A , 69 915-929  
 SALOMON, ALEXANDER, 74 121-127  
 SALZMAN, EMANUEL, 68 788-790  
 SAMADI, A , 71 349-360  
 SAMSON, PAUL C , 73 451-471, 77 561-592  
 SAMUEL, K C , 76 410-425  
 SANDAGE, CURTIS, 61 556-559  
 SANDERSON, STEVENS S , 68 157-164  
 SANDHAUS, HAROLD S , 64 170-181  
 SANDLER, BENJAMIN P , 76 370-387  
 SANDROCK, MARION S , 65 210-214  
 SANDROCK, RACHEL S , 65 210-214  
 SANDS, JAMES H , 66 534-541, 69 58-64  
 SANFORD, JAY P , 73 581-585  
 SANGER, GRANT, 69 618-624  
 SARBER, R W , 59 692-700, 62 418-427, 66 351-356  
 SARIN, L R , 76 410-425  
 SARTWELL, PHILIP E , 59 481-493, 63 608-612  
 SASANO, K T , 59 461-465  
 SASLAW, SAMUEL, 66 588-593  
 SAVAGE, G M , 75 576-583  
 SAXHOLM, ROLF, 69 304-306, 72 98-106, 74 616-621  
 SBAR, SIDNEY, 65 589-595  
 SBARRA, ANTHONY J , 77 669-674, 675-680, 79 810-812  
 SCARBOROUGH, C GERALD, 60 634-638  
 SCHAEDELER, RUSSELL W , 73 781-784, 75 331-337, 359-409  
 SCHAEFER, GEORGE, 70 49-60, 1096-1098, 72 810-824, 75 501-505, 78 697-711  
 SCHAEFER, J ALBERT, 75 638-643  
 SCHAEFER, WERNER B , 65 75-82, 68 273-276, 69 125-127, 70 852-872, 74 683-698, 75 656-658  
 SCHAFF, BURNETT, 61 353-354, 71 429-436, 74 438-440  
 SCHAFFLID, HENRY G , 69 520-512  
 SCHALLEK, WILLIAM, 69 261-266  
 SCHECHTER, M MURRAY, 68 603-614  
 SCHEFF, GEORGE J , 62 374-389  
 SCHEPERS, G W H , 78 512-523  
 SCHERAGO, M , 75 807-822, 77 815-822  
 SCHICK, BELA, 74 (Supplement, August 290-296)  
 SCHLENKER, FRANK S , 75 667-669, 1003-1006  
 SCHLESS, JAMES M , 76 811-831, 80 569-574  
 SCHMIDT, CHARLES E , 71 452-456  
 SCHMIDT, HANS, 61 1-7  
 SCHMIDT, HARMAR W , 78 773-778, 779-784  
 SCHMIDT, HERBERT W , 73 52-60  
 SCHMIDT, L H , 67 798-807, 70 266-273, 74 (Supplement, August 138-152), 75 169-179  
 SCHMIDT, PETER P , 66 594-600  
 SCHNEIDAU, JOHN D , JR , 76 770-788  
 SCHNEIDER, LEO V , 73 966  
 SCHNEIDER, REA M , 76 579-587  
 SCHNITZER, ROBERT J , 65 759-760, 67 674-675, 68 277-279  
 SCHOMER, A , 59 632-635  
 SCHUCK, MILLER H , 68 9-23  
 SCHULMAN, IRVING, 62 618-631  
 SCHULTZ, RICHARD L , 77 536-538  
 SCHURR, ALLAN, 65 511-518  
 SCHWARTZ, ARTHUR, 74 533-540  
 SCHWARTZ, BENJAMIN, 66 594-600  
 SCHWARTZ, EMANUEL, 74 811  
 SCHWARTZ, MORTON, 70 734-738  
 SCHWARTZ, PHILIP, 67 440-452  
 SCHWARTZ, S , 69 1057-1058  
 SCHWARTZ, SEYMOUR I , 76 1063-1070  
 SCHWARTZ, STEVEN O , 60 660-669  
 SCHWARTZ, WILLIAM S , 61 875-880, 64 41-49, 66 436-448, 70 413-422, 924, 76 1097-1099, 79 90-93  
 SCHWARZ, CH , 74 475-476, 77 999-1004, 70 97-101  
 SCHWARZ, JAN, 76 173-194, 77 162-167  
 SCHWEIGER, OTTO, 77 146-154, 78 735-748  
 SCOTT, H WILLIAM, JR , 65 48-63  
 SCOTT, NANCY B , 62 121-127  
 SCOTT, PAUL W , 77 329-337  
 SCOTT, ROBERT A , 77 990-998  
 SCOTT, STEWART M , 76 1002-1006  
 SEABURY, JOHN H , 77 511-515

- SRAGLE, JOSEPH B , 67 311-353  
 STAMAN, JAMES B , 79 681  
 SRGAL, MAURICE S , 69 915-929, 71 210-220,  
 77 1-9, 80 38-45, 46-52, 53-58  
 SRGAL, WILLIAM, 71 112-125, 228-248, 75 495-500  
 STIBERT, FIORUCCI B , 59 86-101, 585-594, 62 67-  
 76, 77-86, 65 201-205, 66 314-334, 71 704-721,  
 73 547-562, 75 601-607  
 SEIBERT, MABEL V , 62 67-76, 73 547-562  
 SEIFE, MARVIN, 63 202-209  
 SEILER, HAWLEY H , 63 81-84  
 SEINFELD, EDWARD, 80 845-848  
 SEIKOFF, IRVING J , 65 102-128, 67 212-216  
 SELIN, MERLE J , 78 944-948, 79 663-665  
 SELKON, J B , 74 (Supplement, August 109-116)  
 SELL, H M , 62 175-180  
 SELLERS, MARGRET IRENE, 76 964-969  
 SELYE, HANS, 67 677-678, 71 319-321  
 SENDERI, MARI, 76 108-122  
 SEN-GUPTA, N C , 66 151-160  
 SEPP, ENDEL, 76 167-172  
 SETTLE, JANET, 70 734-738  
 SEVER, JOHN L , 75 280-294, 76 616-635  
 SEVRINGHAUS, ELMER L , 62 360-373, 68 165-  
 176, 170  
 SEWELL, EDWARD, 66 623-625  
 SEYBOLD, WILLIAM D , 61 193-200  
 SHABART, E J , 76 892-895  
 SHAFFER, MORRIS F , 76 770-788  
 SHAMASKIN, ARNOLD, 62 563-571  
 SHANE, S J , 62 331-332  
 SHAPIRO, ROBERT, 69 1042-1044  
 SHARMAN, I M , 80 223-231  
 SHAUFFER, IRVING, 76 761-769  
 SHAW, CHARLES R , 62 58-66  
 SHAW, J BRIAN, 69 724-733  
 SHAW, K M , 70 274-284  
 SHAW, LAWRENCE W , 68 462-466, 77 877-907  
 SHAW, ROBERT R , 76 970-982  
 SHEEHY, JOHN J , 61 77-94  
 SHEEHY, THOMAS F , JR , 74 835-855  
 SHEETS, LAWRENCE M , 61 369-386, 68 505-522  
 SHELTON, WALTER H , 65 596-602  
 SHELTON, NEIL W , 79 273-283  
 SHEPARD, C C , 77 423-435, 968-975  
 SHEPARD, RICHARD H , 71 249-259  
 SHEPARDSON, H CLARE, 67 544  
 SHER, BEN C , 75 295-302, 77 120-133  
 SHERAGO, M , 76 888-891  
 SHIELDS, D O , 75 53-61, 76 47-63  
 SHIELDS, T W , 78 822-831  
 SHIPMAN, SIDNEY J , 60 788-793, 64 225-248,  
 67 544  
 SHIVPURI, D N , 76 799-810  
 SHOPE, ROBERT E , 79 238-243  
 SHORT, E I , 80 167-180  
 SHULRUFF, ELI, 74 121-127  
 SHULTZ, HENRY H , 77 923-930  
 SHUMAN, CHARLES R , 61 630-641  
 SIBLEY, JOHN C , 62 314-323  
 SIDES, LEROY J , 63 275-291  
 SIEBENMANN, CHARLES O , 68 411-418  
 SIEBENS, ARTHUR A , 69 869-914, 70 672-688,  
 71 676-692, 80 806-824  
 SIEGEL, HENRY, 60 366-376, 70 423-429, 74 972-976  
 SIEKER, H O , 74 309-316  
 SIEMSEN, JAN K , 75 303-318  
 SIFONTES, JOSE E , 67 732-754, 74 (Supplement,  
 August 225-231), 76 388-397  
 SILF, W , 80 (Supplement, July 147-151, 155-156)  
 SILVERMAN, CHARLOTTE, 60 466-482  
 SILVERMAN, GERTRUDE, 61 525-542  
 SILVERMAN, IRVING, 60 354-358, 61 442  
 SILVERMAN, J D , 62 209-212  
 SILVERMAN, MILTON, 62 87-90  
 SILVERTHORPE, M CLARK, 61 525-542  
 SIMINOFF, PAUL, 75 576-583  
 SIMMONS, DANIEL H , 76 195-214  
 SIMMONS, GEORGE, 62 128-143  
 SIMON, THOMAS R , 62 594-609  
 SIMPLER, AGNES THERPSE (SISTER), 76 506-507  
 SIMPSON, DAVID G , 80 426-430  
 SIMPSON, ROBERT M , 60 343-353  
 SINGER, ELLIS P , 76 132-139  
 SINGER, JACQUES, 65 779-782  
 SINGLETON, ALBERT O , JR , 62 439-440  
 SKAGGS, JOSEPH T , 72 647-652  
 SKAVLEM, JOHN H , 68 296-297, 71 163-164  
 SLAVIN, PAUL, 60 755-772, 65 142-158  
 SLOTNIK, IRVIN, 61 742-746  
 SMALL, MAURICE J , 61 893, 63 591-596, 70 191-218,  
 72 386-389, 75 242-258, 77 184-188  
 SMILEY, GEORGE W , 72 647-652  
 SMITH, CARLISLE C , 78 682-691  
 SMITH, C EDWIN, 65 617-626, 67 878-880, 75 199-  
 222  
 SMITH, CHARLES E , 72 64-70, 74 245-248  
 SMITH, C RICHARD, 59 589-598, 63 470-475,  
 70 916-919, 75 618-623, 624-629, 76 752-760,  
 80 216-222  
 SMITH, DAVID T , 62 121-127, (Supplement, July  
 34-47), 64 508-515, 67 201-211, 707-721, 70 547-  
 556, 557-569, 570-576  
 SMITH, DONALD W , 63 372-380, 65 477-480, 69 505-  
 510, 73 529-538, 75 843-845, 77 662-668, 79 94-  
 96, 80 876-885  
 SMITH, GEORGE B , JR , 70 547-556, 557-569  
 SMITH, GRAFTON A , 69 869-914  
 SMITH, I MACLEAN, 75 359-409  
 SMITH, MAPHEUS, 60 773-787  
 SMITH, M I , 59 438-448, 60 62-67, 63 100-107,  
 68 119-126  
 SMITH, MARJORIE M , 66 194-212, 71 308-313,  
 73 768-772, 75 180-198, 76 497-502, 643-659,  
 78 454-461, 570-575

- SMITH, N , 66 125-133, 67 322-340, 69 479-494,  
72 53-63
- SMITH, ROBERT M , 63 4-6, 7-16, 75 576-583
- SMITH, RODNEY P , 69 554-565
- SNELL, W E , 70 755
- SNIDER, GORDON, 64 50-63, 65 93-99
- SNIJDER, J , 78 547-562
- SOBIN, B A , 63 1-3
- SOCHOCKY, S , 78 403-410, 916-920, 79 502-511
- SÜDERHOLM, B , 75 724-729
- SOKOLOFF, MARTIN J , 69 164-172, 73 239-245
- SOKOLSKI, WALTER T , 75 576-583
- SOLOMON, H J , 77 492-495
- SOLOTOROVSKY, MORRIS, 60 366-376, 65 718-721,  
68 212-219, 70 806-811, 74 59-67, 68-71, 72-  
77, 78-83
- SOLTYS, M A , 61 399-406
- SOMMER, GEORGE N J , JR, 67 232-246, 68 782-785
- SOMMERMEYER, LUCILLE, 67 530-534, 68 419-424
- SONES, MAURICE, 62 408-417, 67 671-673
- SOÓS, I , 77 146-151
- SORKIN, E , 67 629-643
- SOTO-FIGUEROA, EVA, 71 704-721, 73 547-562,  
75 601-607, 78 93-100
- SPAIN, DAVID M , 62 144-148, 337-344, 63 339-345,  
65 692-708, 66 621-622, 67 101-102, 68 24-30,  
76 559-567, 79 591-596
- SPARR, HAROLD A , 61 826-831
- SPEARS, R G , 64 516-519
- SPENCE, MARTHA JANE, 69 111-115
- SPENCER, GEORGE E , 62 209-212, 75 833-835
- SPENDLOVE, GEORGE A , 60 628-633
- SPENGOS, THEODORE N , 77 858-862
- SPEYER, JOSEPH F , 75 517-518, 77 501-505
- SPIES, HAROLD W , 69 192-204
- SPINO, PASCAL D , 62 209-212
- SPITZ, LEON J , 66 591-600
- SPIVEY, C G , 80 259-261
- SPORER, ANDREW, 61 508-517
- SPRICK, MARIAN G , 74 552-565
- SPROULE, BRIAN J , 79 315-322
- STÅHLE, INGVAR, 66 271-284, 285-291, 78 368-  
375, 376-390, 79 450-456
- STALLBERG STENHAGEN, S , 75 699-709
- STANDER, HERBERT, 65 761-764, 68 284-285
- STANONIS, DAVID J , 76 852-861
- STARR, PAUL, 80 845-848
- STASKIEI, L I , 79 512-517
- STASKO, IRLAN, 78 931-938, 939-943, 80 274-276
- STAUDT, LOUIS W , 61 705-718
- STAUSS, HANS KARI, 71 473-502, 73 165-190
- STEAD, WILLIAM W , 71 473-502, 529-543, 74 597-  
902
- STEFLE, JAMES H , 77 908-922
- STFLE, JOHN D , 60 383, 62 645-653, 63 76-80,  
64 117-118, 66 261-270, 67 267, 69 636-637,  
71 141-145, 73 960-963, 76 902-905, 77 368
- STEFANIK, W , JR, 59 221, 129-137, 664-673, 664-  
668, 62 101-108, (Supplement, July 22-  
33), 300-306, 63 30-35, 64 87-101, 65 365-  
375, 754-758, 66 194-212, 68 65-74, 548-556,  
70 367-369, 370-372, 375, 714-727, 71 308-313,  
73 72-78, 123-127, 539-546, 768-772, 75 180-198,  
346-347, 510-513, 965-974, 76 497-502, 643-659,  
78 454-461, 570-575, 79 66-71
- STEFFEN, CHARLES G , 69 116-120
- STEFKO, P L , 65 376-391
- STEIN, HANS F , 64 645-658, 67 477-489
- STEIN, HAROLD L , 74 99-105
- STEIN, SAMUEL C , 62 408-417, 66 188-193, 68 695-  
712, 73 239-245
- STEINBACH, M M , 59 624-631, 61 868-874
- STEINBERG, BERNARD A , 65 357-364, 67 351-365,  
366-375
- STEINBERG, ISRAEL, 62 353-359
- STEININGER, WILBUR J , 67 286-291, 292-298,  
69 451-454, 70 518-520, 533-534, 71 766
- STEMMERMAN, GRANT N , 62 324-330
- STEPANYAN, E S , 79 142-151
- STEPHANPOULOS, CONSTANTIN, 76 1079-1087
- STEPHENS, H BRODIE, 60 788-793
- STEPHENS, MARGARET G , 60 487-500, 70 601-609
- STERGUS, INGRID, 75 199-222, 223-241
- STERLING, KENNETH, 62 112-115
- STERN, K F , 75 588-593, 77 976-982
- STERN, KURT, 64 696-697
- STERNBERG, RICHARD O , 77 729-736, 80 249-254
- STEVEN, I , 78 932-933
- STEVENS, ROBERT P , 66 722-731
- STEVIK, CHARLES P , 78 135-137
- STEWART, DOROTHY M , 66 36-43
- STEWART, DONALD B , 69 745-758
- STEWART, SHIRAZ M , 69 611, 73 390-405, 406-421
- STIEF, MARION, 71 478-480
- STIMPLER, F D , 62 418-427
- STINEBRING, WARREN R , 78 712-724
- STINSON, FRANCES LOUISE, 76 896
- STOCKLEN, JOSEPH B , 79 427-439
- STOKES, A M , 62 572-581, 66 16-27
- STOKINGLR, HERBERT L , 60 359-363
- STONE, DANIEL J , 74 533-540
- STONE, MILDRED, 72 633-646
- STONE, WILLIAM F , JR, 61 422-425
- STORFI, CLIFFORD F , 64 327-352, 69 894-914,  
70 672-688, 71 635 667-676-692 72 257-2 7
- STORFI, PATRICK B , 68 769-770, 70 881-894,  
73 117-122, 75 514-516
- STOW, ROBERT M , 61 705-714
- STRAIGHT, CLIFFORD J , JR, 75 638-643
- STRAIN, ANNE K , 79 47-51
- STRANG, VERA G , 76 568-578
- STRALUS, RICHARD I , 63 414-418
- STRIETH, BLAIR B , 77 52-58
- STRIDDER, JOHN W , 63 547-555, 67 21 77 714-  
718
- STRINGER, C J , 69 455-465, 71 85-87,

- STRÖM, LARS, 71 (Supplement, August 28-31)  
 STROMMOR, S., 72 859-862  
 STUART, DOUGLAS G., 70 253-255  
 STUDD, ROBERT S., 69 53-67  
 STEINMAN, IRVING L., 60 357-363  
 SUMIYANO, ICHIRO, 60 359-363  
 SUGA, L., 80 138-140  
 SULLIVAN, B. H., 67 859-868  
 SULLIVAN, I. M., 75 756-767, 78 203-225, 80 571-575  
 SULLIVAN, ROBERT D., 69 957-962  
 SUNDER, I. J., 65 617-626, 67 878-880  
 SUTER, IMANUEL, 60 381, 65 775-776, 69 1050-1052, 70 793-805, 70 17-51  
 SUTHERLAND, IAN, 71 311-315, 317-318  
 SUTHER, W. D., 75 912-920  
 SUYAMOTO, DOROTHY, 69 733-744  
 SWAINACH, W. GEORGE, 76 1063-1070  
 SWARTZ, IRVING B., 61 765-797  
 SWANEY, HENRY C., 60 576-588, 61 569-577  
 SWANEY, JOAN, 61 569-577  
 SWENSON, EDWARD W., 71 676-692, 75 699-709, 710-723, 76 983-987  
 SWIFT, WILLIAM E., JR., 59 102-111  
 SWINDELL, HERBERT, 68 505-522  
 SYPHAX, GRACE B., 70 701-713  
 SZI, KENYU TH. CHIACHI, 71 349-360  
 SZENT GYÖRGYI, NIKDOR, 76 308-311  
 SZYBALSKI, WACIAW, 65 768-770, 68 280-283, 631-633, 69 267-279
- T**
- TABAKIN, BURTON S., 80 825-832  
 TADIR, RODMAN E., 72 801-809  
 TAGGER, MORRIS, 67 538  
 TAKAGAKI, ATSUKO, 77 521-528, 529-535, 78 881-898  
 TAKAII, KENJI, 80 513-553  
 TAKIMURA, YOSH, 75 295-302, 77 120-133  
 TAMURA, MASASHI, 71 165-172  
 TANI, JUNKICHI, 79 738-745  
 T'AO, J. C., 80 359-370  
 TAPLIN, GEORGE V., 79 374-377  
 TARNOWSKI, CURT E., 73 598-600, 76 159  
 TARSHIS, MAURICE, 61 551-556, 65 278-288, 289-301, 302-315, 67 391-395, 72 119-122, 73 601-603, 74 81-91, 78 921-926  
 TASHIRO, K., 78 637-643  
 TATE, K. B., 63 1-3  
 TATSUOKA, MAURICE, 73 172-181  
 TAYLOR, HELEN C., 70 71-90, 72 35-52, 215, 71 7-14  
 TAYLOR, RICHARD R., 77 1023-1025, 79 641-651  
 TAYLOR, ROBERT L., 77 1023-1025  
 TAYLOR, WARREN J., 72 153-161  
 TCHEN, PETER A., 72 179-186, 76 144-151  
 TDESCO, JOSEPH F., 68 393-399  
 TELLESON, W. G., 78 251-258
- TENNANT, CARL W., 62 563-571, 63 295-311, 66 531-541, 69 58-64, 73 117-122, 165-190  
 TERAU, TAKAO, 79 738-745  
 TERMAN, KORNELI, 71 (Supplement, August 7-12)  
 TERNET, ARTHUR A., 68 505-522  
 THATCHER, WILLIAM, 63 667-671  
 THEODOR, PETER A., 65 21-47  
 THIGGS, IRVING M., 71 291-294  
 THOMAS, BERNARD G. H., 65 392-401  
 THOMAS, GORDON W., 63 76-80  
 THOMAS, SIDNEY I., 69 502  
 THOMPSON, BRIAN C., 75 885-896  
 THOMPSON, J. ROBERT, 66 161-174, 69 247-260, 72 155-170, 601-612, 77 931-939, 80 71-77  
 THOMPSON, MILLIE A., 80 216-222  
 THOMPSON, S. A., 78 815-821, 79 773-779  
 THOMPSON, T. L., 74 281-288  
 THOMPSON, ROBERT V., 71 129-136  
 THORPE, MILDRED, 71 142-144  
 THURSTON, JOHN R., 71 119-128, 72 210-217, 633-646, 73 338-350, 563-570, 571-575, 74 756-763, 761-772, 75 958-964, 77 311-322, 79 66-71  
 TICHAIR, CLAUDE, 72 297-329  
 TILFET, WILLIAM S., 76 1-21  
 TIRUNARAYANAN, M. O., 75 62-70, 80 559-568  
 TITSWORTH, E. H., 67 671-675  
 TONIN, C. E., 80 (Supplement, July 50-56)  
 TODA, TADAO, 80 543-553  
 TOGURI, LIZO, 78 927-931  
 TOKUYAMA, GIORGI, 78 871-883  
 TOKUYASU, KIYOTERU, 76 964-969  
 TOMASHEFSKI, JOSEPH F., 71 333-348, 72 479-486  
 TOMPSETT, RALPH, 63 49-61, 64 295-306, 696-697, 69 313-333, 70 91-101, 743-747, 748-754, 72 851-855, 71 (Supplement, August 100-108), 471-473, 572-580  
 TONG, JAMES L., 78 604-609  
 TONG, J. I., 73 930-939  
 TORMA, DAVID M., 67 859-868  
 TOWNIN, MILTON N., 63 295-311  
 TOWNSEND, SAMUEL M., 76 315-319, 79 677  
 TRIVATHAN, ROBERT D., 80 909-910  
 TRIMBLE, HAROLD GUYON, 71 476-478  
 TSAI, SHIH H., 78 106-110, 899-905  
 TSENG, LUN, 68 771-774  
 TSIKOUHAS, EVANGELIOS C., 76 588-600  
 TSUJI, SHUSUKU, 72 393-397, 76 90-102, 77 524-528, 529-535, 78 884-898  
 TSUKAMURA, MICHIO, 75 608-617, 76 298-300, 301-307, 77 346-349, 519-523, 78 121-126, 79 371-373  
 TSUKAWARA, HYOICHI, 74 258-276  
 TUCHMAN, HERMAN, 70 171-175  
 TUCKER, ELON B., 79 344-350  
 TUCKER, HAROLD A., 63 657-666  
 TUCKER, WILLIAM B., 60 715-754, 64 159-169, 70 629-700, 812-810, 72 718-732, 733-755, 756-782, 78 333-345, 832-838

TUKEI, JOHN W , 62 77-86  
 TUNÇIAN, S , 80 410-414  
 TURNBULL, F W A , 73 406-421  
 TURNER, GEORGE C , 60 576-588  
 TURNER, HOWARD G , JR , 68 253-262  
 TURNER, MILLER, 74 464-467  
 TURNER, OTIS D , 68 103-118, 70 593-600, 701-713  
 TUTTLE, WM L , 59 30-38  
 TYLER, FRANK H , 78 682-691  
 TYSAROWSKI, WIESLAW , 80 257-258  
 TYSON, M D , 75 730-744

## U

ULRICH, ELIZABETH W , 75 667-669  
 URBANČÍK, RICHARD, 76 706-707, 78 802-805  
 U S PUBLIC HEALTH SERVICE, 66 632-635, 67 108-113, 553-567, 539-543, 68 264-269, 69 1-12, 70 521-526, 74 196-209, 76 942-963, 80 317-387, 627-640, 757-759  
 USTVEDT, HANS JACOB, 74 (Supplement, August 32-42)  
 UVAROVA, O A , 79 497-501  
 UYEDA, CHARLES T , 80 849-854  
 UYENO, SHIGEICHI, 76 279-285

## V

VAICHULIS, E M K , 80 262-263  
 VALENTINE, ELEANOR H , 78 604-609  
 VANCE, JOHN W , 76 64-75  
 VAN DER HOEVEN, LUDOLPH H , 76 144-151  
 VANDERLINDE, ROBERT J , 61 483-507, 63 96-99  
 VANDIVIERE, H MAC, 65 617-626, 66 95-98, 67 878-880, 77 802-814, 78 799-801  
 VANDRA, EDIT, 78 735-748  
 VAN LIEW, RUTH M , 76 1007-1015  
 VAN ORDEN, L S , 71 743-751  
 VAN ORDSTRAND, HOWARD S , 71 668-675  
 VARDAMAN, THOMAS H , 68 425-438, 439-443, 444-450  
 VARGAS JIMENEZ, FEDERICO, 74 903-916  
 VAUGHAN, GEOFFREY, 76 331-345, 346-359  
 VAUGHAN, LAURENCE H , 72 386-389  
 VELASQUEZ, TULIO, 59 364-390  
 VENKITASUBRAMANIAN, T A , 78 117-120  
 VENNESLAND, KIRSTEN, 59 554-561  
 VERHOEFF, DIRK, 79 357-361  
 VERNES, A , 77 839-847  
 VERSTRAETEN, JEAN M , 67 779-797  
 VESTAL, BETTY L , 80 806-824  
 VETERANS ADMINISTRATION—ARMED FORCES, 72 718-732, 733-755, 756-782, 73 960-963, 74 897-902, 76 360-369  
 VETERANS ADMINISTRATION—NATIONAL TUBERCULOSIS ASSOCIATION, 72 866-868  
 VIEHMAN, ARTHUR J , 70 923  
 VIGIL TARDON, C , 75 345-346

VILLNOW, J , 74 475-476, 77 999-1004, 79 97-101  
 VINDZBERG, WILLIAM V , 68 874-884  
 VINK, H H , 74 633-637  
 VIRÁGH, ZOLTAN, 79 652-658  
 VISCHER, W A , 71 88-96, 97-111, 75 62-70, 80 559-568  
 VISWANATHAN, R , 70 328-333, 73 294-295, 296-300, 78 117-120  
 VITAGLIANO, GUY R , 72 543-547  
 VIVAS, J R , 60 1-14  
 VOGEL, HENRY, 77 823-838  
 VOGEL, R A , 70 498-503, 76 692-696  
 VOLJAVEC, B F , 80 388-397  
 VOLK, BRUNO W , 67 299-321, 70 334-343  
 VOLK, WESLEY A , 73 589-592  
 VORWALD, A J , 62 (Supplement, July 13-21), 455-474, 69 766-789, 841-842  
 VOSSENAAR, TH , 78 547-562  
 VYSNIAUSKAS, CONSTANTINE, 69 121-124, 759-762, 70 536

## W

WAALER, HANS, 74 297-303  
 WADDINGTON, A L , 78 251-258  
 WADE, H W , 68 295-296  
 WADLEY, F M , 60 131-139  
 WAGNER, RAYMOND D , 62 190-208  
 WAGNER, ROBERT R , 68 270-272  
 WAIFE, S O , 65 735-743  
 WAINGORTIN, ERNESTO, 74 277-283  
 WAKSMAN, BRYON H , 68 746-759, 69 1002-1015  
 WAKSMAN, SELMAN A , 60 78-89, 67 261-264, 70 1-8  
 WALDRON EDWARD, DEIRDRE, 74 798-801  
 WALKER, ARTHUR M , 69 854-857  
 WALKER, HASTINGS H , 68 839-862  
 WALKER, RHEY, 66 534-541  
 WALL, NORMAN M , 71 544-555  
 WALLACE, GORDON D , 78 576-582  
 WALLACE, JACK L , 61 563-568  
 WALLACE, STUART, 66 151-160  
 WALLACH, JACQUES B , 73 110-116  
 WALLGREN, ARVID J , 76 715-725  
 WALLNER, LINDEN J , 66 161-174, 69 247-260  
 WALSH, ARTHUR J , 77 952-967  
 WALSH, JOHN J , 72 663-666, 74 464-467, 622-623, 79 251-252, 531-532  
 WALTER, ALBERT, 80 911  
 WALTERS, HENRY W , 68 455-457  
 WALTON, S T , 61 875-880  
 WALZ, DONALD, 69 261-266  
 WANDELT, MABEL A , 70 490-497  
 WARD, D E , 72 659-662  
 WARDRIFF, BUFORD H , 60 634-638  
 WARE, PAUL F , 73 165-190  
 WARING, JAMES J , 61 678-689, 62 (Supplement, July 68-75), 71 616-634, 74 821-829, 75 1-40  
 WARREN, SARAH, 65 627-630



- WARREN, SOL L , 69 153-163  
 WARRING, FREDERICK C , JR , 60 149-167, 63 579-586, 65 235-249, 75 303-318, 80 445-446  
 WASHINGTON, EDWARD L , 59 289-310  
 WASSERBURGER, R H , 74 388-399  
 WASSERMAN, J , 80 19-25, 410-414  
 WASZ-HOCKERT, OLE, 74 471-473, 572-580, 76 256-262  
 WATERMAN, DAVID H , 74 188-195  
 WATSON, DENNIS W , 61 798-808, 63 718-720, 64 602-619  
 WATSON, RAYMOND R , 73 773-775  
 WATSON, T R , JR , 75 730-744  
 WAYNE, LAWRENCE G , 70 910-911, 71 361-370, 73 600-601, 74 376-387, 76 451-467, 468-479, 77 1030-1031, 79 526-530, 80 912-913  
 WEAVER, JOHN, 70 672-688  
 WEBB, CHARLES R , 76 899-901  
 WEBB, GEORGE N , 72 12-34  
 WEBB, WATTS R , 79 780-789  
 WEBSTER, B H , 73 485-500, 76 286-290  
 WECHSLER, HERMAN, 76 909-911  
 WEDIN, DONALD S , 72 64-70  
 WEED, WILLIAM A , JR , 67 391-395, 72 119-122  
 WEIMER, HENRY E , 68 31-41, 594-602, 70 344-348  
 WEINBERG, EUGENE E , 67 503-508  
 WEINBERG, JOSEPH, 60 288-304  
 WEINER, ROBERT S , 74 729-738  
 WEINSEL, MAX, 64 50-63  
 WEINSTEIN, S B , 72 345-355  
 WEISEL, WILSON, 61 474-482, 742-746, 71 573-583, 73 773-775  
 WEISER, ORMAN L , 69 58-64, 464-468, 73 117-122, 77 1023-1025  
 WEISER, RUSSELL S , 64 669-674, 68 564-574, 69 406-418  
 WEISS, CHARLES, 63 694-705  
 WEISS, DANIEL L , 75 954-957, 76 507-508, 78 793  
 WEISS, DAVID W , 73 781-784, 77 719-724, 79 813-815, 80 340-358, 495-509, 676-688  
 WEISS, WILLIAM, 62 160-169, 307-313, 64 64-70, 65 735-743, 69 396-405, 844, 72 268-273, 75 319-325, 76 897-898, 78 17-20, 79 537-540  
 WEISSMAN, HERMAN, 64 572-576, 73 853-867, 76 1088-1093  
 WELCH, EDWARD J , 67 94-100  
 WELLER, L E , 62 475-480  
 WELLS, A Q , 66 28-35, 69 479-494, 72 53-63  
 WELLS, WILLIAM F , 75 420-431  
 WERNER, CHARLES A , 63 49-61  
 WERNER, GEORGES H , 69 473  
 WERNER, WILLIAM A , 67 514-516  
 WERTMAN, DANIEL E , 77 32-38  
 WESSERMAN, EDWARD, 78 815-821  
 WEST, ANN F , 80 398-403  
 WHALEN, JOSEPH W , 71 382-389  
 WHARTON, DWIGHT J , 80 188-199  
 WHITCOMB, FRANCES C , 68 727-733, 71 762-764  
 WHITCOMB, WALTER H , 78 391-398  
 WHITE, ARTHUR C , 77 134-145, 80 12-18, 443-444  
 WHITE, F CLARK, 62 107, 72 274-296, 79 134-141  
 WHITE, ROBERT G , 70 793-805  
 WHITESIDE, ELEANOR S , 69 419-442  
 WHITFIELD, GEORGE B , 75 584-587  
 WHITNEY, JACK M , 76 852-861  
 WHITTAKER, CHARLES KEITH, 70 920-921  
 WHITTENBERGER, JAMES L , 72 453-464  
 WHORTON, MERRILL C , 65 596-602  
 WIDELOCK, DANIEL, 67 598-603, 68 290-291, 734-738, 69 1022-1028, 70 349-359, 363-366, 728-733, 1042-1053, 71 305-307, 841-859, 72 143-150, 246-251, 74 293-296, 428-437, 75 41-52, 76 732-751, 78 788-792  
 WIER, JAMES A , 73 117-122, 75 921-937, 76 811-831, 77 749-763, 80 259-261, 569-574  
 WIESE, E ROBERT, 63 480-486  
 WIGGINS, MILTON L , 69 818-823  
 WILEY, L J , 79 541  
 WILKING, VIRGINIA N , 66 63-76  
 WILL, DRAKE W , 61 226-246, 76 435-450  
 WILLETT, HILDA POPE (*see also* POPE, HILDA), 80 404-409  
 WILLIAMS, JAMES H , 65 511-518, 519-522  
 WILLIAMS, JOHN H , JR , 72 107-116, 76 360-369  
 WILLIAMS, MARVIN L , 62 549-554  
 WILLIAMS, M HENRY, JR , 78 173-179, 80 689-699, 700-704  
 WILLIAMS, ROBERT O , 76 660-668  
 WILLIAMSON, JAMES, 77 623-643  
 WILLIS, GERTRUDE MITCHELL, 76 1049-1062  
 WILLIS, H STUART, 61 387-398, 62 (Supplement, July 76-79), 64 113-116, 66 95-98, 73 291-293, 74 793-795, 77 802-814  
 WILLIS, MYRON J , 69 234-240, 78 667-681  
 WILLISTON, ELIZABETH H , 59 336-353, 62 156-159, 481-483  
 WILMER, HARRY A , 69 847-851  
 WILSON, F JEAN, 65 187-193  
 WILSON, GEORGE C , 73 351-361  
 WILSON, GEORGE M , 78 604-609  
 WILSON, HENRI M , 68 615-621  
 WILSON, MICHAEL M , 65 187-193  
 WILSON, NORMAN J , 60 406-418, 704-705, 68 874-884  
 WILSON, RUSSELL H , 68 177-187, 70 296-303  
 WILT, KENNETH E , 77 62-72  
 WINDER, FRANK, 71 785-798, 73 779-780, 75 476-487  
 WINFIELD, DON L , 70 476-482  
 WINGO, CHARLIE F , 76 660-668  
 WINSTEN, SEYMOUR, 70 806-811, 74 59-67, 72-77  
 WINTER, WILLIAM J , 61 171-184  
 WINTERSCHIED, LOREN C , 67 59-73, 68 625-628  
 WISELOGLE, FREDERICK Y , 60 121-130  
 WITHERINGTON, DEXTER T , 71 892-893  
 WITTKOWER, ERIC D , 67 869-873, 71 201-219

WOJWOD, A J, 72 123-125  
 WOLD, DEWITT E, 71 415-453  
 WOOLSON, IRVING N, 67 103-105  
 WOLINSKI, EMANUEL, 59 221, 62 300-306, 61 87-101, 65 365-375, 751-758, 66 194-212, 68 65-74, 548-556, 70 367-369, 375, 714-727, 71 308-313, 73 72-78, 539-516, 768-772, 75 180-198, 510-513, 965-971, 76 197-502, 613-659, 77 168-171, 78 570-575, 80 269-273, 522-531  
 WOLOCZOW, H, 79 541  
 WONG, HARRY LOUMAN, 75 118-152  
 WOOD, LAWRENCE E, 69 227-233, 231-210, 73 917-929, 78 667-681  
 WOODBURY, JOHN W, 60 648-653  
 WOODHAM, GEORGE D, 75 919-953  
 WOODRUFF, C EUGENE, 59 391-401, 60 794-800, 61 269, 387-398, 62 555, 63 140-149, 64 620-629, 66 151-160, 67 286-291, 292-298, 68 583-593, 69 451-454, 70 518-520, 533-534, 71 766, 75 975-986, 80 445  
 WOODS, FRANCIS M, 68 902-911  
 WOODWARD, THEODORE E, 71 592-595  
 WOOLF, A L, 59 311-316  
 WOOLF, C R, 74 511-532, 80 705-715  
 WOOLF, VICTOR F, 59 679-686  
 WORKMAN, JOHN M, 75 823-827  
 WORSSAM, ANTHONY R H, 73 726-734  
 WORTMAN, H C, 60 520-523  
 WRIGHT, GEORGE W, 60 706-714  
 WRIGHT, JEANNE E, 59 494-510  
 WRIGHT, KENNETH W, 67 652-656, 74 128-135, 79 72-77  
 WRIGHT, NOBLE M, 74 638-640  
 WRIGHT, R R, 79 212-220  
 WRINKLE, CAROLYN K, 66 99, 69 599-603  
 WU, JACK FOY, 63 710-713  
 WU, NANCY, 71 693-703  
 WUNDERLICH, GOOLOO S, 80 371-387  
 WYATT, JOHN P, 80 (Supplement, July 94-103)  
 WYBORNEY, V J, 75 854-855  
 WYLIE, ROBERT H, 61 465-473, 74 351-357  
 WYNN-WILLIAMS, N, 69 724-732

## Y

YALE, HARRY L, 65 357-364, 67 354-365, 366-375  
 YAMAMOTO, MASAKUNI, 79 371-373  
 YAMAMURA, YOSHIIHIRE, 79 738-745  
 YAMAMURA, YUICHI, 75 99-104, 77 482-491, 79 738-745, 80 240-248, 535-542, 911  
 YAMAURA, KENJI, 80 543-553  
 YANG, STEPHEN C H, 61 648-661  
 YANNAKOS, D, 72 527-536  
 YANNITELLI, S A, 59 391-401, 60 794-800  
 YARD, ALLAN S, 73 956-959

YASAKA, SHIGERU, 75 99-104  
 YATER, WALLACE W, 71 904-924  
 YATES, J LEWIS, 69 216-226  
 YEAGLE, ROBERT L, 65 519-522, 523-546, 635-636  
 YFGIAN, DIRAN, 61 483-507, 63 96-99, 64 81-86, 65 181-186, 66 11-51, 629-631, 68 557-563, 71 860-866, 72 539-512, 73 586-588, 75 781-792, 76 272-278  
 YERUSHALMI, J, 61 443-461, 64 225-248, 249-255  
 YIN, S C, 71 417-427, 468-470  
 YOSHIMURA, TETSUYA, 80 543-553  
 YOUATT, JEAN, 78 806-809  
 YOUMANS, ANNE STEWART, 63 25-29, 64 534-540, 541-550, 69 790-796, 72 196-203, 73 764-767, 80 750-752, 753-756  
 YOUMANS, GUY P, 59 336-352, 61 407-421, 569-577, 62 156-159, 62 181-483, 63 25-29, 64 534-540, 541-550, 66 416-435, 486-496, 69 790-796, 72 196-203, 73 637-649, 764-767, 75 280-294, 76 616-635, 77 301-310, 450-461, 462-472, 80 153-166, 750-752, 753-756  
 YOUNG, A C, 73 330-337  
 YOUNG, HENRY, 73 868-881  
 YOUNG, J M, 67 385-390  
 YOUNG, R C, 79 468-473  
 YOUNG, ROBERT J, 72 204-209, 76 225-231  
 YU, PAUL N G, 62 29-44, 79 265-272  
 YUE, WEN Y, 78 899-905

## Z

ZAHN, DANIEL W, 59 636-642, 69 351-369, 74 445-453, 75 644-647  
 ZAJCEW, W, 78 411-425  
 ZAPPASODI, PETER, 72 297-329, 79 152-179, 180-203  
 ZARAFONETIS, CHRIS J, 71 220-227  
 ZAROWITZ, HAROLD, 60 801-807  
 ZASLY, LOUIS, 74 624-632  
 ZEIDBERG, L D, 65 111-127, 70 360-362, 1009-1019, 75 111-121  
 ZIEVE, LESLIE, 64 159-169  
 ZIMMERMAN, H M, 62 586-593  
 ZINNEMAN, HORACE H, 74 773-782, 76 247-255, 78 832-838  
 ZINS, EUGENE I, 60 206-211  
 ZISKIND, JOSEPH, 80 (Supplement, July 104-112)  
 ZISKIND, MORTON M, 68 382-393  
 ZITRIN, CHARLOTTE MARKER, 74 15-28, 76 256-262  
 ZOHMAN, LENORE R, 78 173-179, 80 689-699, 700-704  
 ZORINI, A OMODEI, 78 485-487  
 ZOUMBOULAKIS, D, 72 527-536, 73 964-965, 74 (Supplement, August 197-208)  
 ZUCKERMAN, ANNE, 64 318-321  
 ZWERLING, HENRY B, 64 225-248, 249-255

# INDEX OF SUBJECTS

## A

- Abortion and tuberculosis, 70 49-60
- Abcess(es)
  - cold, spontaneous, of chest wall, 62 (Supplement, July 18-67)
  - pulmonary
    - acute, 61 171-181, 69 673-681
    - pancreatic deoxyribonuclease in, 76 1-21
    - in tularemia, (case reports) 65 627-630
- Abstracting philosophy, (editorials) 62 116-118
- (1) Acetylamino benzal thiosemicarbazone *See* Thiosemicarbazones
- Achylasia, (case reports) 76 180-190
- Acid(s)
  - amino
    - metabolism, detected in urine from tuberculous patients, (Notes) 76 867-870
    - relation to problem of host resistance to tuberculosis, (Notes) 66 378-380
    - of urinary excretion
      - in normal subjects on controlled diets, 60 439-447
      - in tuberculous subjects on controlled diets, 60 448-454
  - ascorbic
    - tuberculininhibitory properties and inhibition of tubercle bacilli by urine, 69 406-418
    - in tuberculosis, 61 381-393
  - fatty
    - in calf lung, effect on tubercle bacilli, 75 630-637
    - in rabbit tissue, resistance of tubercle bacilli, 69 710-723
  - heterocyclic, hydrazides and derivatives in experimental tuberculosis, 67 366-375
  - isonicotinic, hydrazide *See* Isoniazid
  - logic, as inhibitor of tubercle bacilli, 61 739-741
  - para-aminosalicylic *See* Para aminosalicylic acid
  - phthienoic, and related acids, cellular reactions, 65 655-672
- Acid-fast bacilli *See* Bacilli and Tubercle bacilli
- Acidosis, respiratory, induction by oxygen breathing, 77 737-748
- Acoustic basis of chest examination, 72 12-31
- ACTH *See* Hormones, corticotropin
- Actinomycetales *See* Fungi
- Actinomyces *See* Mycoses
- Addison's disease, with histoplasmosis and pulmonary tuberculosis, (case reports) 72 675-684
- Adenitis, tuberculous
  - mediastinal and hilar, 76 799-810
  - treatment of, report by ATS Committee on Therapy, 68 302-305
- Adenoma *See* Tumors
- Adenomatosis *See* Tumors, adenomatosis, and carcinoma, alveolar
- Adolescents, nutrition and tuberculosis in, 74 (Supplement August, 173-183)
- Adrenocortical function
  - and tuberculosis sensitivity, 73 795-804
  - in tuberculosis, pulmonary, 64 630-644, 66 364-372
  - during isoniazid therapy for, 70 841-851
  - relationship with stress and, 69 351-369
- Adrenocorticotrophic hormone *See* Hormones, corticotropin
- Aerosol, amphotericin B used as, (Notes) 80 441-442
- Agar diffusion
  - precipitation techniques, in determining mycobacterial antigenic relationships, 73 637-649
  - double, in tuberculosis, 77 162-172
- Aged persons
  - resection in, 73 10-51
  - tuberculin sensitivity in, 75 161-168
  - skin, 77 323-328
- Agglutination, collodion, effect of histoplasmin skin tests, 66 588-593
- Agitator, for bacteriologic specimens, (Notes) 70 176-177
- Agranulocytosis
  - due to amithiozone, (case reports) 65 339-343
  - during streptomycin treatment of military tuberculosis, 59 317-324
- Air *See also* Pulmonary function
  - embolus during pneumoperitoneum, (case reports) 72 537-538
  - flow, physics of, in emphysema, 80 (Supplement, July 123-125)
  - hygiene in tuberculosis, 75 420-431
  - pollution and bronchitis, (editorials) 80 582-584
  - travel in tuberculosis, 61 678-689
  - velocity index, 62 17-28
  - ways, chronic obstruction of, pulmonary diffusion in, 71 249-259
- Air borne infection in rabbits, 73 315-329
- Alaska, histoplasmin sensitivity of natives, (Notes) 79 542
- Alcohol, effect on tubercle bacilli in sputum, 68 419-424
- Alcoholism in the tuberculous before and during hospitalization, (editorials) 79 659-662
- Aldinamide<sup>®</sup> *See* Pyrazinamide

- Allergens, acid fast, methods for comparison of potency, 60 131-139
- Allergy (ies)  
 effect of isoniazid on, 71 (Supplement, August 197-208)  
 in emphysema, 80 (Supplement, July 181-183)  
 to isoniazid, (case reports) 71 783-792  
 to para-aminosalicylic acid, 65 235-249  
 relationship to gross lung disease, 78 226-234
- Milescheria boudii* See Fungi
- Alloxan induced diabetes in albino rats, compared with cortisone treated tuberculosis, 65 603-611
- Alpha-ethyl-thioisonicotinamide, experiments on antituberculosis activity of, 79 1-5
- Alveolar cell carcinoma See Tumors, carcinoma
- Alveolar proteinosis, pulmonary See Alveolus
- Alveolus(i)  
 chronic emphysema of, in horse, 80 (Supplement, July 141-143)  
 pulmonary proteinosis of, (case reports) 80 249-254  
 respiratory surface, effective, and other pulmonary properties in normal persons, 70 296-303
- Amberson, J Burns, lecture, 74 821-829, 76 931-941, 78 499-511, 80 315-325  
 notes on (ATS), 71 980-983
- Ambulatory patients  
 tuberculous  
 chemotherapy in, 70 1030-1041, 75 41-52  
 with "open-negative" syndrome, 78 725-734
- American Trudeau Society  
 Amberson lectures, opening remarks on, 74 980-983  
 Annual Meetings, abstracts of medical papers presented at, (1958) 78 285-328, (1959) 79 822-850  
 award of the Trudeau medal, 67 114-119, 68 808-811, 72 559-565, 74 647-649, 76 1112-1116, 78 957-959  
 award of the Will Ross medal for 1954, 72 566-568  
 changes ahead, (editorials) 75 648-649  
 Charles J Hatfield lecture, introduction, 76 920-921  
 coronary arterial disease, symposium, 71 904-924
- DIAGNOSTIC STANDARDS AND CLASSIFICATION OF TUBERCULOSIS of National Tuberculosis Association, history of, 65 494-504
- formula for determining irregular discharge rates, 78 959-960
- manual for consecutive case conference (Pembine type), 79 258-262
- methods for determining susceptibility of tubercle bacilli to streptomycin, dihydrostreptomycin, and PAS, 65 105-108
- necrology, 67 122, 705, 75 698, 77 874, 80 122
- notices, 63 230, 623 624, 64 125-126, 223, 476, 579-582, 65 109-110, 219-220, 504, 652-653, 66 117, 260, 389, 508, 649, 781-782, 67 120-121, 270-271, 396-397, 550, 574, 68 306, 502, 654, 837, 972, 69 148, 317, 477, 655, 858, 1071, 70 380, 515, 759, 952, 1111, 71 160, 332, 464, 607, 771, 925, 72 140, 256, 417, 710, 73 156, 313, 449, 74 167, 307, 484, 652, 984, 75 168, 355, 528, 697, 1018, 76 166, 328, 513, 713, 928, 1117, 77 200, 373, 560, 728, 875, 1036, 78 150, 329, 496, 659, 814, 960, 79 118, 263, 397, 549, 697, 851, 80 123, 282, 455, 597, 764, 924
- obituaries, 67 398, 551, 68 154, 69 649, 70 187, 543, 71 326, 73 310, 790, 74 163, 650, 818, 75 352, 859, 76 326, 711, 927, 77 371, 78 146, 490, 79 118, 394, 695, 80 120, 452, 453, 921
- organization and committee structure,  
 1953-1954, 69 131-142  
 1954-1955, 71 148-159  
 1955-1956, 73 145-151  
 1956-1957, 75 157-167  
 1957-1958, 77 191-199  
 1958-1959, 79 108-117
- panel discussions  
 on changing concepts and modern treatment of tuberculosis, 70 930-948  
 on chemotherapy of tuberculosis, 67 680-697  
 on giving pneumoperitoneum or pneumothorax, 68 954-971  
 on present concepts of antimicrobial therapy in pulmonary tuberculosis, 68 819-836  
 on survival and revival of tubercle bacilli in healed tuberculous lesions, 68 477-495  
 on therapy of miliary and meningeal tuberculosis, 68 636-653
- Pembine Conferences, reports on  
 Eighth, 65 786-791  
 Ninth, 68 496-501  
 Tenth, 70 184-186  
 Eleventh, 72 137-139  
 Twelfth, 73 973-975  
 Thirteenth, 76 164-165
- postgraduate courses in pulmonary disease, 59 111-112
- preliminary program of annual meeting, medical sessions, (1958) 77 553-559, (1959) 79 387-393
- present objectives and policies in the field of medical education, the role and

*American Trudeau Society, cont*

- responsibility of the Committee on Medical Education, 69 143-147
- production and distribution of BCG vaccine in the U S A , 65 647-648
- reports
  - of Clinical Subcommittees
    - on current status of drug therapy in tuberculosis, 61 436-440
    - on German experience with thiosemicarbazone, 61 145-157
    - on streptomycin in the treatment of tuberculosis, 59 106-110
  - of Clinical and Laboratory Subcommittees, 63 496-500, 65 100-108
  - of Committee on Medical Research, 1951-1952, 66 503-505, 1952-1953, 68 812-816
  - of Committee on Therapy and of Laboratory Subcommittee of Committee on Medical Research, 65 351-355
  - of Committee on Therapy to Committee on Medical Research, 66 641-646, 68 946-949, 69 313-315, 69 1068-1069, 70 540-542
  - of Director of Medical Education, 70 1105
  - of Executive Secretary, 70 1105-1106
  - of Fellowship Board of Committee on Medical Research, 1951-1952, 66 506-507, 1952-1953, 68 816-818
  - of Interim Committee on DIAGNOSTIC STANDARDS, 68 150-152
  - on isoniazid toxicity, by Committee on Therapy, 68 302-305
  - of the Laboratory Subcommittee of Committee on Medical Research and Therapy, and of Subcommittee on Evaluation of Laboratory Procedures of Committee on Revision of DIAGNOSTIC STANDARDS, 61 274-298
  - of Laboratory Subcommittee to Committee on Medical Research, 66 647-648, 68 951-953, 69 316
  - on projects for the recovering tuberculosis patient
    - in some European countries, 66 104-108
    - in the United States, 67 693-703
  - on pyrazinamide, by Committee on Therapy, 75 1012-1015
  - on resections of residual necrotic lesions, by Committee on Therapy, 67 268
  - of (Dr H McLeod) Riggins, chairman of Committee on Medical Research and Therapy, read at the Annual Meeting, April 24-28, 1950, 62 556-561
  - on sections of the American Trudeau Society, 70 1107-1109
  - by Subcommittee on Clinical Classification of Committee on Revision of DIAGNOSTIC STANDARDS, on classification of pulmonary tuberculosis, 61 760-763
  - of Subcommittee on Pulmonary Function Tests, 62 451-454
  - on treatment of tuberculous lymphadenitis, by Committee on Therapy, 70 949-951
  - at Veterans Administration Thirteenth Conference on Chemotherapy of Tuberculosis, 69 854-857
  - request for data on effects of cortisone-corticotropin on tuberculosis in humans, by Committee on Therapy, (correspondence) 64 471-472
  - statements
    - on BCG, 60 681-682
      - role in prevention of clinical tuberculosis, 78 145
    - by Committee on Administrative Problems, recommendations for use of vacant tuberculosis beds, 76 922-926
    - by Committee on Medical Research
      - clinical significance of *in vitro* determinations of streptomycin susceptibility and resistance, 65 103-105
      - criteria for "negative" sputum in patients following antimicrobial therapy, 65 102-103
    - by Committee on Radiation Effects, chest roentgenogram and chest roentgenographic surveys related to X-ray radiation effects and protection from radiation exposure, 80 115-117
    - by Committee on Therapy
      - antimicrobial therapy of tuberculosis, 72 408-416, 78 656-658
      - BCG in prevention of clinical tuberculosis, 78 145
      - bed rest in treatment of tuberculosis, 69 1069-1070
      - cycloserine, 75 1016-1017
      - effect of cortisone and/or corticotropin on tuberculous infection in man, 66 254-256
      - genitourinary tuberculosis, 72 413-415
        - in female genital tract, 75 524-527
      - indications for adjunct corticotropin and corticosteroid therapy in tuberculosis, 76 708-710
      - need for rest therapy in connection with long courses of drug treatment for pulmonary tuberculosis, 67 679
      - the "open-negative" problem, 80 118-119
      - present status of excisional surgery in treatment of pulmonary tuberculosis, 72 416

*American Trudeau Society, statements, cont*

- present status of skeletal tuberculosis, 74 814-817
- problem of so called "good chronic" case of pulmonary tuberculosis, 64 643-646
- recommended standards for home care of patients with tuberculosis, 78 655-656
- role of Committee on Therapy in the American Trudeau Society, 66 644-646
- treatment of tuberculous meningitis, 70 756-758
- by Committees on Therapy and on Administrative Problems, acceptable standards in the treatment of tuberculosis, 73 607-608
- by Executive Committee, the chest roentgenogram and chest roentgenographic surveys related to X-ray radiation effect and protection from radiation exposure, 77 203-208
- by Laboratory Subcommittee, hypopharyngeal (laryngeal) swabbing for the cultural diagnosis of pulmonary tuberculosis, 73 970-972
- by Subcommittee on Pulmonary Function, 73 152-155
- streptomycin-tuberculosis research project, 59 140-167
- tuberculosis hospital medical and administrative standards, 72 699-709
- tuberculosis mortality among residents of large cities (1947-1949), 66 109-116
- "Tuberculosis A World-Wide Problem" conference, papers from (November 18, 1958), 79 684-694
- Amines, primary, simple, *in vitro* and *in vivo*, 61 407-421
- Amino acid *See* Acids
- (4)-Amino-4' B hydroxyethylaminodiphenyl sulfone *See* Hydroxyethyl sulfone
- Aminophylline as bronchodilator agent, 77 729-736
- Amithiozone *See* Thiosemicarbazones
- Amphotericin B
  - as aerosol, (Notes) 80 441-442
  - serum concentrations in man, (Notes) 77 1023-1025
- Amylase, content of pleural fluid in pancreatitis and other diseases, 79 606-611
- Anaphylaxis, to viomycin, (case reports) 75 135-138
- Anemia
  - aplastic, following use of streptomycin-PAS, (case reports) 68 455-457
  - hemolytic, following treatment with PAS, (case reports) 76 862-866
  - sickle cell, and hepatic tuberculosis, (case reports) 67 247-257
  - and tuberculosis, 65 735-743
- Anergy, in tuberculous patients
  - changes in tuberculin sensitivity when treated with antimicrobial therapy, 67 286-291
  - and prolongation of life, 67 292-298
- Aneurysm, Rasmussen's, in pulmonary tuberculosis, 60 589-603
- Angiocardiography in artificial pneumothorax, 62 353-359
- Angiography in advanced pulmonary tuberculosis, 71 810-821
- Angiopneumography and bronchography in tuberculous fibrothorax, 73 61-71
- Anomaly
  - of the lung and bronchial tree, 64 686-690
  - vascular, and lung cysts, (case reports) 71 573-583
- Anorexia, treatment with insulin, 60 25-31
- Anthracite coal miners *See* Pneumoconioses
- Anthracosilicosis *See* Pneumoconioses
- Antibacterial agents
  - active against tubercle bacilli in seed plants, 62 475-480
  - and isomazid resistance, (Notes) 68 283
- Antibiotics *See* Antimicrobials and specific names of drugs
- Antibody(ies) *See also* Hemagglutination
  - antituberculous
    - masked, 72 345-355
    - studies, 72 210-217
  - circulating, to tuberculosis, demonstration of clinical studies, 75 954-957
  - technique, 75 949-953
  - hemagglutination test, 65 194-200
    - and its hemolytic modification in tuberculosis, 65 194-200
    - slide-test modifications, against tubercle bacilli, 63 667-671
  - interference by tuberculo-protein and polysaccharide in pulmonary tuberculosis, 73 547-562
  - lung specific, in rabbits, 78 259-267
  - protective, in tuberculosis, 76 256-262
  - tuberculous
    - by agar diffusion, 74 229-238, 239-244
    - in human serum, 74 239-244
    - in rabbit serum, 74 229-238
- Antigen(s)
  - BCG extract, from sheep erythrocytes, 75 958-964
  - fungal, sensitivity to, in students, 73 620-636
  - mycobacterial, serologic investigations of, 73 563-570, 571-575, 74 756-763, 764-772, 75 958-964
  - PPD and others, prepared from atypical acid-fast bacilli and *Nocardia asteroides*, 79 284-295

## Antituberculous

tuberculin treated *ex-thoracis*, in eliciting cutaneous hypersensitivity to tuberculin, (Notes) 61 322

Antituberculous effect on tuberculin reaction, 59 701-706, 60 351-358, 811, (correspondence) 61 112-735-737, 62 325-531, (editorials) 555

Antimicrobials *See also* Chemotherapy, Drugs, and specific drugs

## activity

influence of nitrogen on, 67 503-508

of viomycin, 63 7-16

## effect

on atypical mycobacteria, 78 151-161

on microbial cells 76 1031-1048

first seven years, 72 110-152

Antimicrobial therapy *See also* Chemotherapy

of anergic and partially anergic tuberculous patients, response to changes in tuberculin sensitivity, 67 286-291, 292-298

of pulmonary tuberculosis, comparison of effect of four variables, 72 718-732

of isoniazid, streptomycin, and PAS as two drug regimens, 72 776-782

of three streptomycin PAS regimens, 72 733-755

Antituberculous compounds, *in vitro* activity of, 66 210-227

Antituberculous drugs *See also* Chemotherapy, Drugs, and specific names of drugs

bactericidal activities, 71 (supplement, August 109-116)

Antituberculosis treatment, effectiveness, tested by direct culture of bacilli in patient's blood, (Notes) 80 85-88

Aorta, abdominal

hemorrhage into jejunum through tuberculous lymph nodes, (case reports) 65 210-211

tuberculous arteritis of, with rupture into duodenum, (case reports) 60 801-807

Aplastic anemia *See* Anemia

Appendicitis

during pneumoperitoneum treatment, 61 333-354

tuberculous, 61 182-191

Arcana of tuberculosis Parts I and II, 78 151-172, Part III, 78 126-153, Part IV, 78 383-603

Armed Forces, Selective Service registrants with tuberculosis, 80 795-805

Army, streptomycin regimens in, study of, (July 1916-April 1919) 60 715-751

Arterial alveolar oxygen tension gradient, in pulmonary disease, 69 71-77

Arteriosclerosis, obscure pulmonary, and right heart failure (Ayerza's disease), car-

dine cirrhosis with, (case reports) 70 1083-1091

Arteritis, tuberculous, of aorta, with rupture into duodenum, (case reports) 60 801-807

Arteries (ies)

coronary, surgical approach to disease of (symposium), 71 901-921

innominate and subclavian aneurysms, (case reports) 70 700-708

pulmonary

agents in circulation of, (case reports) 70 611-651

pressure, and frequency of postprimary pulmonary tuberculosis, 78 536-546

Ascorbic acid *See* Acid

Asparaginase of mycobacteria, (Notes) 70 920-921

Asparagine, utilized by *M. tuberculosis* for growth, 68 127-135

Aspen *See* United States, Colorado

*Aspergillus fumigatus* *See* Fungi

*Aspergillus* infestation *See* Fungi

Asphyxia fatal, from Lucite plumbage, 61 422-425

Atelectasis

basal linear, after phrenic nerve interruption, 65 88-92

segmental, in children with primary tuberculosis, 70 597-605

Atherosclerosis, coronary (symposium), 71 901-921

Aureomycin *See* Chlorotetracycline

Auscultation, 60 639-647

acoustic basis of chest examination, 72 12-34

Ayerza's disease, and cardiac cirrhosis, (case reports) 70 1083-1091

## B

B663, *See* Phenazine

Bacillus(i)

acid fast

atypical, 73 351-361, (Notes) 80 431-437

PPD and other antigens prepared from, 70 284

in sputum of patient with pulmonary lesions, 75 199-222

chromogenic

from human sources, (correspondence) 73 601-603

culture, 65 278-288

hypersensitivity, 65 302-315

pathology, 65 289-301

oxygen requirements, 69 604-611

response to antimicrobial agents on glycerol blood agar medium, (Notes) 72 119-122

susceptibility to chemotherapy, (Notes) 76 697-702

*Bacillus(s), acid fast, cont*

- cultural studies, 76 103-107, 108-122
  - human, nontuberculous, penicillin susceptibility in, (Notes) 75 675-677
  - from human sources, (correspondence) 72 695-698
  - methods of testing virulence, 62 632-637
  - nonpathogenic for guinea pigs, 73 351-361, (correspondence) 74 478-480
  - nontuberculous, from humans, bacteriologic studies, (Notes) 76 683-691
  - report of panel, 72 866-870
  - sputum examination, 59 449-460
  - "wax" in guinea pig sensitization, 69 241-246
  - "yellow" in human infection, 73 917-929
  - Calmette-Guérin *See* BCG, Tubercle bacilli
  - tubercle *See* Tubercle bacilli
  - yellow, pathogenicity of, 71 74-87
- Bacterial resistance, incidence, encountered with tuberculosis chemotherapy regimens employing isoniazid and isoniazid-streptomycin, (Notes) 67 106-107**
- U S Public Health Service cooperative clinical investigation, (editorials) 70 739-742
- Bacteriophage, temperate, from *M butyricum*, 80 232-239**
- Bacterium(a)**
- acid-fast, metabolism of
    - Krebs cycle in acetate oxidation pathways of, 71 266-271
    - and *Mycobacterium*, 71 260-265
  - transformation, not induced by desoxyribonucleic acid, (Notes) 80 911
- Baldwin, Edward R., (editorials) 62 (Supplement, July 1-2)
- Ballistocardiogram, after artificial pneumoperitoneum, in chronic pulmonary diseases, 66 52-57**
- Barbiturates, effect on isoniazid toxicity, (Notes) 66 100-103**
- BCG**
- allergy, isoniazid effect, 77 232-244
  - American Trudeau Society statements, 60 681-682, 78 145
  - crude extracts, biologic activity, (Notes) 78 939-943
  - effect of bile, 59 102-105
  - extract antigens in detection of homologous antibodies, 74 756-763, 764-772
  - fatal tuberculosis induced by, 70 402-412, (correspondence) 71 321-323, 73 301-305
  - harvesting and dispensing apparatus, (Notes) 63 613-614
  - immunization, lack of circulating antibodies after, by globulin titration, (Notes) 78 793
  - immunizing activity, affected by isoniazid, (Notes) 75 650-655
  - immunizing properties compared with an isoniazid-resistant mutant of *M tuberculosis*, (Notes) 70 527-530
  - infection
    - in guinea pig, cortisone in, 69 511-519
    - from injection, (correspondence) 72 869-870
  - inoculation in children, reactions, 74 (Supplement, August 32-42)
  - and irradiated antituberculosis vaccine, in experimental tuberculosis in guinea pigs, 67 341-353
  - method of obtaining, (correspondence) 79 105
  - and *M tuberculosis*, metabolism of isoniazid by, (Notes) 78 806-809
  - preservation by freeze-drying, (Notes) 65 344-346
  - production, new method, (Notes) 64 698-701
  - report of ad hoc advisory committee to Surgeon General (1957), 76 726
  - role in prevention of clinical tuberculosis, 78 145
  - specificities of aqueous and saline extracts, 73 563-570, 571-575
  - standardization, (correspondence) 65 641
  - strain, cultivation of, (Notes) 78 934-938
  - studies, (Notes) 68 462-466
  - substrains, differential characteristics *in vivo* and *in vitro*, 74 655-666, 667-682, 683-698, 699-717
  - Tice strain, (correspondence) 75 692-693
  - tuberculin reaction variation after, 60 541-546
  - use and value, 76 715-525
  - vaccination
    - community trials, 77 877-907
    - correlation of tuberculin reaction with pulmonary lesions in persons with and without, 68 713-726
- cortisone and isoniazid in, 76 263-271
- effect**
- and hyaluronidase, 64 442-447
  - on mice infected with tuberculosis, 68 451-454
  - of guinea pigs
    - by multiple puncture method, 60 547-556
    - sonic fragility of leukocytes from, 79 323-328
  - in humans, followed by hemagglutination reaction, 66 58-62
  - immunologic aspects, (editorials) 60 670-674
  - as index of familial susceptibility to tuberculosis, 69 383-395
  - and influence on tuberculin test, 72 35-52
  - lymphatic calcification after, 73 239-245
  - and measles, (case reports) 72 228-230
  - of mice, 75 624-629



BCG, *see* *cont*

- microscopy and culture of *M. tuberculosis* in, 79 181-191
- in Panama, (Notes) 67 522-525
- properties, and isoniazid-resistant mutant in guinea pigs, (Notes) 75 656-658
- pulmonary lesions in persons with and without, 68 695-712
- in rabbit tissues, 72 310-311
- in sarcoidosis, 62 108-117
- in silicosis, 62 155-171, 69 763-789
- in Sweden, (correspondence) 79 678-679
- tuberculin
  - allergy after, 70 1061-1082
  - compared in persons with and without, 70 71-90
  - fraction
    - purified, from unheated cultures, 69 300-303
    - for testing vaccinated subjects, 66 335-341
  - and sensitivity in Hong Kong, 76 215-224
  - of tuberculous children, serum protein electrophoretic pattern and Middlebrook-Dubos titer, (Notes) 79 522-524
  - and Vole, 71 (Supplement, August 43-50)
- vaccine
  - bacterial count, vital staining method, (Notes) 78 785-787
  - effect
    - of age and temperature, 68 96-102
    - of time and temperature on antigenic potency, 70 873-880
  - fresh, frozen, and dry, antigenic activity, 63 85-95
  - and hyaluronidase, synergistic effect in guinea pigs, 68 188-198
  - progress toward standardization, (editorials) 79 80-82
  - viability, (Notes) 63 714-716
    - influence of methods of preparation, (Notes) 61 695
    - new method of counting organisms, (Notes) 79 816-817
  - virulence, 59 567-588
- Bed rest, modified
  - in minimal tuberculosis, 61 809-825, 67 401-420
  - in pleural effusion, 67 421-431
  - on recovery from pulmonary tuberculosis, and physical activity, 75 359-409
- Beds, hospital, for tuberculous patients, ATS statement on, 76 922-926
- Bellevue Hospital (New York City), chest service (Amberson Lecture), 74 821-829
- Bellows apparatus in pulmonary function studies, 80 724-731
- Benemid® *See* Probenecid

- Benzalkonium chloride in isolation of *M. tuberculosis*, (Notes) 71 284-288
- resistance to, 70 312-319
- in tuberculosis bacteriology, (Notes) 80 912-913
- Benzoate, action in tubercle bacilli, 69 705-709
- Benzoyl PAS
  - inhibiting isoniazid inactivation in man, 80 26-37
  - metabolism, biochemical aspects, (Notes) 75 1003-1006
- Beryllium *See* Pneumoconiosis
- Bile, effect on BCG, 59 102-105
- Biochemistry in analysis of virulence of tubercle bacilli, 80 535-542
- Biology of tuberculosis, 68 1-8
- Biopsy (ies)
  - bronchial, preoperative, in pulmonary tuberculosis, 78 839-847
  - laryngeal, during chemotherapy, 69 247-260
  - of lung, 71 668-677
  - needle, of the parietal pleura in tuberculosis, 78 17-20
  - pericardial, 75 469-475
  - pleural, for effusions, 78 8-16
  - scalene node, 68 505-522
- Blastomyces dermatitidis *See* Fungi
- Blastomycosis *See* Mycoses
- Blebs, subpleural, surgery of, 79 577-590
- Blood *See also* Serology, Serum cells
  - red *See* Erythrocytes
  - white *See* Leukocytes
- of cold blooded animals, mycobacteria in, 77 823-838
- direct culture of bacilli in, as drug therapy test, (Notes) 80 85-88
- flow, through nonventilated portions of lung, 68 177-187
- iodine, effect of Dionosil® on, 77 181-183
- layering, in dog heart, 70 570-576
- media, for culturing tubercle bacilli, 64 551-556
- PAS in, 76 1071-1078
  - buffered, concentration studies, (Notes) 72 543-547
  - effect of probenecid on, 66 228-232
- pyrazinimide spectrophotometric determination in, 75 105-110
- serum
  - concentrations, attained with PAS-ascorbate, 76 880-887
  - in pulmonary tuberculosis, protein bound carbohydrates of, 75 793-806
- vessels, histologic study of, in resected tuberculous lungs, 64 489-498
- "Bluing" phenomenon, contamination source in tubercle bacilli cultures, (Notes) 80 95-99

- Body build, in relation to tuberculosis morbidity, 76 517-539
- Boeck's sarcoid *See* Sarcoidosis
- Bone  
grafts, homogenous, ribs from thoracoplasty as possible source, 63 210-212  
marrow, tubercle bacilli in, 63 346-354  
tuberculosis, in children with primary and miliary tuberculosis, 75 897-911
- Books  
Achievements of BCG Vaccination By GERHARD HERTZBERG, 60 675  
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AND JAMES BORDLEY, 73 142
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JACOB JESSE SINGER, 63 494
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390
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AND L HENRY GARLAND, 74 304
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682
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69 130
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80 279-280
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and Practitioners By PHILIP  
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tion By HENRY J MEYER AND EDGAR  
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*et al*, 68 472
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MAURICE Z COOPER, 74 481
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361
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RAPPORT AND HELEN WRIGHT, 69  
129
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tion Bronchologique By JEAN  
IONNOU, L DUCHET-SUCHAUX, AND  
A PINELLI, 78 653
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64 121
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zation of the Tuberculous By  
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- Report of the Committee on Rehabilitation Needs of the Patients in Public Tuberculosis Hospitals in Upstate New York, 65 347
- Report on Tuberculosis in British Zone of Germany with a Section on Berlin, Made in September-October 1947 by M DANIELS AND P D'ARCY HART, Report on Tuberculosis in Germany (U S Zone) by commission appointed by Secretary of the Army, composed of ESMOND R LONG, PHILIP E SARTWELL, SILAS B HAYS, AND ALONZO W CLARK, 59 713
- Respiratory Diseases and Allergy By JOSEF S SMUL, 69 647
- Respiratory Disease and the General Practitioner By C W C TOUSSAINT, 79 106
- Roentgen Signs in Clinical Diagnosis By ISIDORE MESCHAN, 76 512
- Roentgenanatomische Grundlagen der Lungenuntersuchung By F KOVÁTS, JR, AND Z ZSEBOK, 73 447
- Roentgenology of the Chest Edited by COLEMAN E RABIN, 78 812
- Sandoz Atlas of Haematology, 72 134
- Sectional Radiography of the Chest By IRVING J KANE, 68 944
- Segmental Anatomy of the Lungs By EDWARD A BOYDEN, 75 349

*Books, cont*

- Selected Experiments in Medical Microbiology  
By STEWARD M BROOKS, 79 107
- Skeletal Tuberculosis By VICENTE SANCHIS-OLMOS, 60 145
- Social-Medical Investigations on Tuberculosis in the County of Hordaland By K ENGEDAL, 77 725
- Socio-Economic Conditions and Tuberculosis Prevalence, New York City, 1949-1951 By ANTHONY M LOWELL, 75 521
- Das Sogenannte Alveolarzellenkarzinom By HERMANN ECK, 77 725
- La Souche du BCG By A FRAPPIER AND M PANISSET, 79 819
- Spontanheilungen der Lungentuberkulose By LASAR DUNNER, 74 978
- Staphylococcal Infections By IAN MACLEAN SMITH, 80 113-114
- Streptomycin, Its Nature and Practical Applications Edited by SELMAN A WAKSMAN, 61 897
- Streptomycin and Dihydrostreptomycin in Tuberculosis Edited by H MCLEOD RIGGINS AND H CORWIN HINSHAW, 60 815
- Studier over Urogenitaltuberkulosens Behandlung By KARL OLA F OBRANT, 70 181
- Studies in Tuberculosis By R G FERGUSON, 74 161
- Subphrenic Abscess By H R S HARLEY, 75 1009
- Surgery of the Chest By JULIAN JOHNSON AND CHARLES K KIRBY, 71 462
- Surgery of Pulmonary Tuberculosis By JAMES H FORSEE, 71 768
- Surgery in Tuberculosis By RICHARD H OVERHOLT AND NORMAN J WILSON, 72 255
- Surgical Disorders of the Chest Second edition By J K DONALDSON, 59 717
- Surgical Extrapleural Pneumothorax By DONATO G ALARCON, 62 229
- Surgical Management of Pulmonary Tuberculosis No 1, The John Alexander Monograph Series Edited by JOHN D STEELE, 78 488
- Surgical Treatment for the Abnormalities of the Heart and Great Vessels By ROBERT E GROSS, 64 704
- Syllabus of Laboratory Examinations in Clinical Diagnosis Edited by THOMAS HALE HAM, 64 124
- Symposium on Coal Miner's Pneumoconiosis, 69 309
- Les Symptomes de la Tuberculose Pulmonaire et de ses Complications Clinique, Physiologique, Pathologique, Therapeutique By EDOUARD RIST, 63 360
- Synopsis of Medical Entomology By V E BROWN, 70 927
- Textbook of Medicine Eighth edition Edited by RUSSELL L CECIL AND ROBERT F LOEB, 65 348
- Textbook of Medicine Ninth edition Edited by RUSSELL L CECIL AND ROBERT F LOEB, 72 695-696
- Textbook of Medicine Tenth edition Edited by RUSSELL L CECIL AND ROBERT F LOEB, 80 761-762
- Therapie der Lungentuberkulose By E HESSE, 71 903
- Therapy of Fungus Diseases Edited by THOMAS H STERNBERG AND VICTOR D NEWCOMER, 76 161-162
- The Therapy of Skin Tuberculosis Translated and revised by ERNEST A STRAKOSCH, 73 447
- This is Your World By HARRY A WILMER, 68 299
- Thoracic Surgery By RICHARD H SWEET, 63 725, 70 378
- Thoracic Surgery and Related Pathology By GUSTAF E LINDSKOG AND AVERILL A LIEBOW, 70 179
- Thoracic Surgical Patient By LEW A HOCHBERG, 69 129
- Topographische Ausdeutung der Bronchien im Roentgenbild By CLAUS ESSER, 77 189
- Tracheotomy A Clinical and Experimental Study By THOMAS G NELSON, 79 256
- Treatment of Respiratory Emergencies Including Bulbar Poliomyelitis By THOMAS C GALLOWAY, 68 943
- Tubercle Bacillus and Laboratory Methods in Tuberculosis By M A SOLTYS, C A ST HILL, AND I ANSELL, 68 475
- Tubercle Bacillus in the Pulmonary Lesion of Man By GEORGES CANETTI, 72 555-558
- Die Tuberkulosebekämpfung in der Schweiz Edited by H BIRKHAUSER, 72 557-558
- Tuberculose Primaire Chez l'Enfant By RAYMONDE GRUMBACH, 74 812
- Tuberculose Pulmonaire et Pleurale By PIERRE-BOURGEOIS, 70 926
- Tuberculosis *British Medical Bulletin*, vol 10, no 2, 1954 Edited by J G SCADDING, 71 324

*Books, cont*

- Tuberculosis A Global Study in Social Pathology By JOHN B McDougall, 63 493
- Tuberculosis in Animals and Man A Study in Comparative Pathology By JOHN FRANCIS, 79 682
- Tuberculosis and Aspiration Liver Biopsy Its Clinical Significance in Diagnosis and Therapy By A J CH HAEN AND CORNELIA VAN BEEK, 72 557
- Tuberculosis in Childhood and Adolescence By F J BENTLEY, S GRZYBOWSKI, AND B BENJAMIN, 71 605
- Tuberculosis Classification Pathogenesis and Management By MILOSH SEKULICH, 73 143
- Tuberculosis in History By LYLE S CUMMINGS, 61 592
- Tuberculosis in Ireland Report of the National Tuberculosis Survey MEDICAL RESEARCH COUNCIL, 72 405
- Tuberculosis Nursing Instruction in Universities for Public Health Nursing Students By JEAN SOUTH, 67 881-882
- Tuberculosis in Obstetrics and Gynecology By GEORGE SCHAFER, 75 349-350
- Tuberculosis Treated with Streptomycin By E T BERNARD, B KREIS, AND A LOTT, 62 228
- Tuberculosis in White and Negro Children, vol I The Roentgenologic Aspects of the Harriet Lane Study By JANET B HARDY, 78 952
- Tuberculosis in White and Negro Children, vol II The Epidemiologic Aspects of the Harriet Lane Study By MIRIAM E BRAHMY, 78 952
- Tumeurs Broncho-Pulmonaires Exposé Anatomique Clinique By A POLICARD *et al*, 74 645
- Tumors of the Lungs and Mediastinum By B M FRID, 80 113
- Über den Einfluss von Physikalischen und Chemischen Faktoren auf die Cytoplogie der Tuberkelbazillen und Anderer Mykobakterien By WILHELM ROTH, 79 545
- Unsere Erfahrungen über die Moderne Behandlung der Milchartuberkulose und der Meningitis Tuberculosa im Kindesalter By J R WERNER AND K KUMIN, 78 135
- Vaccination Against Tuberculosis By L SULLIVAN and co workers, 74 160
- Vers la Médecine Sociale By RENE SAND, 60 146-147
- Veterans Administration Hospitals Number, the Medical Clinics of North America, January, 1950, The Major Pulmonary Diseases BENJAMIN B WELLS AND MARC J MISLER, Consulting Editors, 80 762
- When Doctors Are Patients By MAX PINNER AND BENJAMIN F MILLER, 65 636
- White Plague By RENE AND JEAN DUBOS, 68 803
- Wish I Might By ISABELL SMITH, 73 305
- X-Ray Diagnosis of Chest Diseases By Coleman R Rabin, 68 295
- Yearbook of Drug Therapy Edited by HARRY BECKMAN, 80 919-920
- The Year Book of General Surgery—1958-1959 Series Edited by MICHAEL E DEBAKEY, 80 504-505
- You and Tuberculosis By JAMES E PERKINS AND FLOYD M FELDMAN, in collaboration with RUTH CARSON, 67 547
- You're Human, Too! By ADRIAN STRIFELSMAN, 61 121
- Your World and Mine By HALBERT L DE VRIES, 75 857
- $\beta$  Propylalbutylamine, (Notes) 76 1074-1076
- Brain, tuberculoma of, 62 654-665
- Breast, tuberculosis, 73 810-821
- Breathing *See also* Pulmonary function  
energy cost and control, in chronic pulmonary emphysema, 80 (Supplement July 131)
- mechanics of  
gas exchange and pulmonary circulation, in influence of ventilatory mechanics, 80 53-58
- physical properties of lung, 80 38-45
- respiratory work, 80 46-52
- positive pressure, intermittent  
in bronchopulmonary disease, 71 693-703
- in pulmonary emphysema, 76 33-36
- in pulmonary tuberculosis, 72 473-481
- Bronchial stenosis *See* Stenosis
- Bronchial tree experimental exploration by tracheal fenestration 78 815-821
- Bronchial tuberculosis *See* Tuberculosis
- Bronchial ulceration *See* Ulceration
- Bronchiectasis  
in ambulant clinic series, 77-78
- apical, tomographic comparison of the lesion 74 288-291
- bronchography in pulmonary tuberculosis 74 74-72
- cardiopulmonary function in patients with chronic bronchitis and emphysema 77 17-24
- clinical course, 76 74-75



*Bronchiectasis cont*

- and postoperative lung function, 77 209-220
- prognosis, 66 457-476
- as related to bronchogenic carcinoma, 64 620-629
- and tuberculosis, relation between, 61 387-398
- Bronchioles, carcinoma arising from, 63 399-416
- Bronchitis
  - air pollution and, (editorials) 80 552-584
  - chronic, (Notes) 75 340-342
  - as etiologic factor in obstructive emphysema, 80 (Supplement, July 185-193)
  - physiologic defects in, 78 191-202
  - prevalence, nature, and pathogenesis of, 80 483-494
  - syndrome, and chronic emphysema, symposium on, Aspen (Colorado), June 13-15, 1958, 80 (Supplement, July 1-213)
  - tuberculous, in pulmonary resection, 61 185-192
- Bronchocavitary junction, effect of streptomycin on, in relation to cavity healing, 67 173-200
- Bronchodilation, in bronchopulmonary disease, 71 693-703
- Bronchogenic carcinoma *See* Tumors
- Bronchogenic tuberculosis *See* Tuberculosis
- Bronchograms, under hypnosis, (Notes) 79 525
- Bronchography
  - and angiopneumography, in tuberculous fibrothorax, 73 61-71
  - in bronchiectasis, pre- and postoperatively, 69 657-672
  - 3,5-diiodo-4-pyridone N-acetic acid in, 74 178-187, 188-195, 77 32-38
  - effect on blood iodine, (Notes) 77 181-183
  - and histopathologic correlation, in tuberculosis, 73 681-689
  - in pulmonary tuberculosis, 64 394-407, 70 274-284
  - before surgery, 77 561-592
  - with iodized oil, 66 699-721
  - simplified, (Notes) 66 246-250
  - and tomography, in apical bronchiectasis, 74 388-399
  - with water soluble contrast medium, 68 760-770
- Broncholithiasis, 73 19-30
- from histoplasmosis, (case reports) 77 162-167
- Bronchopulmonary disease
  - cytologic patterns in, 77 22-31
  - positive pressure and bronchodilation in, 71 693-703
- Bronchoscopy
  - bronchial perforation during, (case reports) 78 106-110
  - review of, 61 355-368
  - in tuberculosis, primary, of childhood, 74 (Supplement, August 267-278)
  - in tuberculous lesions, (Notes) 73 586-588
  - value of sputum examination after, (Notes) 77 716-718
- Bronchospirrometry
  - complications after, (Notes) 66 244-245
  - investigations before and after resection and lobectomy for pulmonary tuberculosis, 75 710-723
  - study of pulmonary function after decortication, 66 509-521
  - during thoracic surgery, differential function in, 75 730-744
  - before and after thoracoplasty, 75 724-729
  - values, significance of, 75 699-709
  - vital capacity in, (Notes) 76 320-321
- Bronchostenosis, bilateral, tuberculous, in patient with normal roentgenographic findings, (case reports) 63 706-709
- Bronchus(1)
  - adenoma of 75 865-884
  - carcinoma of
    - with laryngeal carcinoma, (case reports) 74 438-440
    - and pneumonia, in adults, 76 47-63
    - and pulmonary tuberculosis, 73 853-867
    - in relation to calcified nodules in lung, 66 151-160
    - and silicosis, (case reports) 76 1088-1093
  - disease of
    - bronchographic-histopathologic correlation in, 73 681-689
    - in lungs resected for pulmonary tuberculosis, 68 657-677
  - endo-, hamartoma of, (case reports) 80 65-70
  - erosion, caused by calcified lymph node causing hemoptysis, (case reports) 65 206-209
  - major, complicated by secondary infection, carcinoma arising from, 63 255-274
  - minor, carcinoma arising from, 63 399-416
  - mucoid impaction, 76 970-982
  - papilloma of, (case reports) 78 916-920
  - papillomatosis of, (case reports) 71 429-436
  - perforation, during bronchoscopy, (case reports) 78 106-110
  - reconstruction, plastic, 64 477-488
  - regenerative versus atypical changes in, 79 591-596
  - resected, and postoperative complications, 74 874-884
  - supernumerary, and bronchial adenoma, (case reports) 75 326-330
  - tracheal, anomalous, to the right upper lobe, (case reports) 64 686-690

*Bronchus(s), cont*

## tuberculous

in dog, 73 748-763

lesions, intra- and extraluminal, 74 (Supplement, August 256-266)

"quiescent," 73 451-471

*Brucella abortus*

infection in mice, 73 251-265

in relation to *M. tuberculosis*, (correspondence) 74 478*Brucella suis*, vaccines from gamma-irradiated, and from *M. tuberculosis*, (Notes) 79 374-377

Brucellosis, human, caseation necrosis, (case reports) 67 859-868

*Bulla(e)*

## emphysematous

complicated by hemorrhage and infection, surgical drainage of, (case reports) 61 742-746

infected, (case reports) 61 742-746, (case reports) 69 287-296

surgery, 74 856-873

**C**<sup>14</sup>C-labeled PAS-isoniazid, 75 71-82

C-reactive protein, in pulmonary tuberculosis, (Notes) 74 464-467

## Calcification(s)

intracranial, after tuberculous meningitis

in children, 78 38-61

serous, (case reports) 78 101-105

pulmonary, disseminated, 62 1-16

scalene node biopsy in patients with, 72 91-97 and tuberculin, histoplasmin, and coccidioidin sensitivities in Rocky Mountain area, 59 643-649

in pulmonary nodule, solitary, (case reports) 74 106-111

of regional lymph nodes, following BCG vaccination, 73 239-245

as related to bronchogenic carcinoma, 64 620-629

tuberculous, renal, (case reports) 71 437-440

Calcium benzoyl-PAS, (Notes) 75 667-669

and calcium PAS, tolerability of, 79 351-356

Cancer *See also* Tumors and specific organs

detected in tuberculosis surveys, 62 491-500 of lung, 70 763-783

cytologic diagnosis, 61 60-65

*Candida albicans* *See* FungiCaplan's syndrome *See* Pneumoconoses

Carbohydrates, protein bound, of blood serum in pulmonary tuberculosis, 75 793-806

Carbolfuchsin, staining of mycobacteria in diagnostic films, 74 597-607

Carbon dioxide narcosis, treated by resuscitator, 74 309-316

Carbon isotopes, in *M. tuberculosis*, 71 609-615

Carbon monoxide diffusing capacity during exercise, 74 317-342

Carboxide<sup>®</sup> gas, for decontamination of articles made by tuberculous patients, 71 272-279Carcinoma *See* TumorsCardiac symptoms *See* Heart

Cardiopulmonary disease, smoking in, 77 10-16

Cardiopulmonary function

in Boeck's sarcoid, cortisone in, 67 154-172

in bronchiectasis, preoperative and postoperative, 69 869-914

in chronic obstructive emphysema, 80 689-699

in hematogenous pulmonary tuberculosis in patients receiving streptomycin, 64 583-601

in pulmonary fibrosis, 80 700-704

Cardiospasm, simulating mediastinal tumors, (case reports) 63 597-602

Caseation necrosis, in brucellosis, (case reports) 67 859-868

Case finding *See also* Surveys

in general hospitals, 70 304-311

and tuberculin test, (Notes) 79 378-381

in general population, schools, and hospitals, 80 (Supplement, October 73-93)

in psychiatric hospitals, resurvey interval of, (Notes) 79 537-540

in tuberculosis, 71 406-418

in Erie County (New York), 59 78-85

by tuberculin testing, 78 667-681

Caseous-pneumonic tuberculosis *See* Tuberculosis

Cats in experimental tuberculosis, treated with isoniazid, 65 376-391

## Catalase

## activity

correlated with isoniazid resistance and guinea pig virulence, (Notes) 72 246-251

of isoniazid resistant tubercle bacilli, (Notes) 69 471-472

of isoniazid susceptible and resistant strains of *M. tuberculosis*, (Notes) 79 669-671of *M. tuberculosis*, 78 735-748of *M. tuberculosis* H37Rv, (Notes) 80 257-258

of tubercle bacilli, 76 1007-1015

in bovine liver, inhibited by isoniazid, trace metals in, (Notes) 77 501-505

colorimetric test in *M. tuberculosis* cultures, (Notes) 71 305-307

enzyme, of mycobacteria, 77 146-154

in isoniazid resistance 73 72-774

peroxidase and isoniazid relation in mycobacteria, 75 42-70

- Cattle erythrocytes, PPD sensitization of, (Notes)  
77 177-180
- Cavity (ies)  
coccidioidal, recurrent, after surgery, (case reports) 71 131-136
- cystlike  
in drug tested rabbits, 75 965-974  
in drug-treated tuberculosis, 77 221-231  
in tuberculosis during isoniazid therapy, (Notes) 69 1054-1055
- healing at bronchoesophageal junction, streptomycin effect, 67 173-200
- inspissated, prognosis, 59 53-67
- in noninfectious patient, resection for, 74 169-177
- nontuberculous, in experimental tuberculosis, produced by egg albumin, 75 99-101
- "open negative," problem of, (ATS) 80 118-119
- persistent, and noninfectious sputum during chemotherapy, and relationship to "open healing," 75 242-258
- home care in, 77 764-777
- pulmonary  
in anthracosis, 71 541-555  
in development of streptomycin resistance, 59 391-401  
from *Histoplasma capsulatum*, (case reports) 69 111-115  
in lower lobe, 63 625-643  
roentgenographic simulation of, 71 529-543  
tension, (correspondence) 77 368  
pathogenesis and treatment, 76 370-387  
in tuberculosis, chemotherapy and phenomenon of open cavity healing, (editorials) 71 441-446
- tuberculous  
gaseous content, 80 1-5  
giant  
healing, (Notes) 78 140-144  
surgery, 77 593-607  
"open healing," 72 601-612, 75 223-241, 242-258  
under chemotherapy, (case reports) 73 944  
in resected specimens, 72 153-170
- Cell(s)  
alveolar, carcinoma, 79 502-511  
cultures, mycobacteria in, 77 789-801
- HeLa  
atypical mycobacteria in, 77 968-975  
growth characteristics of acid-fast microorganisms other than tubercle bacilli in, (Notes) 80 744-746
- M. tuberculosis* in, 77 423-435
- lysis, in tuberculin sensitivity, 68 746-759
- mammalian, and mycobacteria in tissue culture, (correspondence) 75 347-348
- mycobacterial, crude, biologic activity of, (Notes) 80 274-276
- sonic treated, in transfer of tuberculin hypersensitivity, 73 246-250
- tuberculin sensitized, inhibition of, *in vitro*, 80 410-411
- Centrifugation, for concentrating tubercle bacilli, (Notes) 76 899-901
- Cerebellopontine angle, tuberculoma of, simulating acoustic neuroma, (case reports) 63 227-229
- Cerebral vessels, thrombosis of, with necrosis of the basal nuclei, 61 247-256
- Cerebrospinal fluid, in tuberculous meningitis, transfer of glucose into, 67 732-754
- Charcoal  
diluent, for tubercle bacilli, 70 989-994
- medium  
for tubercle bacilli, 70 955-976, 71 382-389  
drug susceptibilities, (Notes) 71 447-451
- Chemoprophylaxis  
in chronic obstructive pulmonary emphysema, 80 716-723  
and inhibition of immunity, 74 541-551  
with isoniazid, in experimental tuberculosis, (correspondence) 74 475-476  
in tuberculosis, (editorials) 74 117-120, 80 648-658 (Supplement, October 1-21)
- Chemotherapy *See also* Antimicrobials, Drugs, and specific drugs  
of actinomycosis, 63 441-448  
antituberculosis, dynamics of, 74 (Supplement, August 100-108)  
in conjunction with surgery, (correspondence) 74 476-478  
cross-resistance of *M. ranae*, 69 267-279  
effectiveness, shown by use of guinea pig omentum, 68 583-593  
healing process, 79 497-501  
natural, (editorials) 76 669-670  
of tuberculous open cavity, (case reports) 73 944-955  
in histoplasmosis, 75 912-920  
of leprosy, evaluation of drugs, 69 173-191  
of miliary and meningeal tuberculosis in the adult, 69 912-925  
of nocardiosis, 63 441-448  
original, of noncavitary pulmonary tuberculosis, isoniazid and isoniazid-PAS in, 80 641-647  
of photochromogenic mycobacterial infections, 80 522-534  
in pneumoconiosis, complicated by tuberculosis, (correspondence) 79 818  
and pneumothorax, antagonistic effect, (correspondence) 70 533-537, (correspondence) 71 600-602, 766

*Chemotherapy, cont*

prolonged, causing drug resistance of tubercle bacilli, (Notes) 76 871-876

relapse of tuberculous lesions during and after, 80 (Supplement, October 47-71)

resistance of tubercle bacilli to drugs, 61 483-507

and tuberculin sensitivity in rabbits, 79 329-338

of tuberculosis, 61 407-421, 79 492-496

  active, (correspondence) 63 490-492

    cycloserine-isoniazid in, (Notes) 80 89-94

    arrested in guinea pigs by reinfection, 80 554-558

  clinical and histopathologic study of, 69 247-260

  with Conteben®, 61 20-38

  experimental, 60 223-227, 64 541-550

    heterocyclic acid hydrazides and derivatives, 67 366-375

    isoniazid and derivatives, 67 354-365, 68 411-418

in mice, 69 104-110

  action of streptomycin-PAS in, (correspondence) 60 808-810

  intrapertitoneal infection in screening of drugs, 69 280-286

hospital and home in, 80 (Supplement, October 23-45)

in infants and children, 74 (Supplement, August 225-231)

intestinal, as prophylaxis, 64 430-441

long-term, and prognosis, (correspondence) 70 178

primary

  in children, 69 682-689

    segmental lesions in, 756-763

  and prognosis, (correspondence) 70 535-536

pulmonary

  and ambulation, 70 1030-1041, (correspondence) 71 602-603

  effect on healing rate, 76 988-1001

  fibrocaseous, chronic, relapse rates after, (Notes) 71 302-304

  isoniazid with PAS-pyridoxine, (Notes) 78 773-784

  lesions after, 71 165-185

  phenomenon of open cavity healing, (editorials) 71 441-446

  prolonged indefinitely, 70 219-227

  relationship to surgery, 80 (Supplement, October 95-115)

  roentgenographic spread, during sanatorium residence before, 68 863-873

  streptomycin plus isoniazid-PAS-pyridoxine, 78 779-784

  renal, urine cultures during, 70 149-154

  sulfones in the mouse, 63 556-567

  of tuberculous meningitis, 69 192-204

  in children, 76 832-851

  of tuberculous patients

    nonhospitalized, 70 1042-1053, 75 41-52

    noninfectious, to prevent relapse, (correspondence) 80 108

  viability of tubercle bacilli with and without, (Notes) 67 874-877

## Chest

examination, acoustic basis, 72 12-34

lesion

  asymptomatic and circumscribed, 62 512-517

  undetected in mass surveys, 64 249-255

roentgenograms

  in Baroness Erlanger Hospital (Chattanooga, Tennessee), 60 377-382

  interpretation of, 64 225-248

surgery *See* Surgery, Thoracoplasty

survey *See* Roentgenography

taping, 76 167-172

wall

  spontaneous abscesses, 62 (Supplement, July 48-67)

  tuberculous sinuses, 66 732-743

## Chick embryo(s)

extract, failure to accelerate growth of tubercle bacilli, (Notes) 65 783-785

mycobacteria in, 73 276-290

and *M. tuberculosis*

  virulence, 74 249-257

  yolk sac method for isolating, (Notes) 77 511-515

Children *See also* Infants

antihistamine medication on tuberculin reaction in, 60 354-358

school-age, Liberian, tuberculin patch-test survey among, (Notes) 67 665-668

tuberculin tests in, 60 45-50

tuberculosis in, 74 (Supplement, August 1-6)

  hemagglutination reaction, 70 139-148

  miliary and meningeal, streptomycin-promizole® therapy for, 61 159-170

primary

  chemotherapy, 69 682-689, 79 756-763

  value of follow-up studies, 64 499-507

  streptomycin-resistant tubercle bacilli in, 66 63-76

of tuberculous patients, risk of developing tuberculosis among, 70 1009-1019

## China, chest survey, 72 356-366

## Chlortetracycline

antituberculous activity of, 72 367-372

in pulmonary tuberculosis, 59 624-631, 61 875-880

*Chlortetracycline, cont*

- tuberculostatic activity *in vitro* and *in vivo*, (correspondence) 59 221, 60 143
- Cholecystitis, tuberculous, (case reports) 70 734-738
- Choleraesuis infestation, with cystic disease, (case reports) 71 92-98
- Chromogens, acid-fast, in gastric juice of non-tuberculous patients, (correspondence) 79 543-544
- Circulation
  - dynamics in pulmonary emphysema, during exercise, 80 (Supplement, July 128)
  - pulmonary
    - arterial, effects of alteration, on tuberculosis in monkeys, 65 48-63
    - capillary, 71 822-829
- Cirrhosis, cardiac, with obscure pulmonary arteriosclerosis and right heart failure (Ayerza's disease), (case reports) 70 1083-1091
- Cleavage, metabolic, of antituberculous thioethyl compounds, 74 78-83
- Clinic, chest, hemoptysis in patients of, 63 194-201
- Coal miners *See* Pneumococcosis, anthracite
- Coccidioidial cavity *See* Mycoses
- Coccidioidial granuloma *See* Mycoses and Tumors
- Coccidioides immitis* *See* Fungi
- Coccidioidin *See* Fungal antigens
- Coccidioidomycosis *See* Mycoses
- Coenzymes I and II *See* Pyridine nucleotides
- "Coin lesions"
  - simulated by fibrin bodies, (case reports) 72 659-662
  - of lung, (Notes) 73 134-138
- Collagen, of lung, 80 (Supplement, July 45-48)
- Collapse
  - pulmonary, electrocardiographic changes after, 64 50-63
  - therapy, in tuberculous psychotic patients, 67 232-246
- Collodion agglutination *See* Agglutination
- Colorado, Aspen
  - "first" conference, postscript to, 80 (Supplement, July 213)
  - Symposium on Emphysema and the "Chronic Bronchitis" Syndrome (June 13-15 1958), 80 (Supplement, July 1-213)
- Communicability, of histoplasmosis, 63 538-546
- Compounds, antituberculosis, chemotherapeutic decomposition, (Notes) 73 593-596
- Concentration agents, lethal action on tubercle bacilli in sputum, 69 991-1001
- Contagiousness of coccidioidomycosis, 61 95-115
- Conteben® *See* Thiosemicarbazones
- Cor pulmonale
  - polycythemia, and idiopathic hypoventilation, (case reports) 80 575-581
  - after resection, 77 387-399
- "Cord factor"
  - relation to pathogenicity, 77 482-491
  - of tubercle bacillus
    - isolated from petroleum-ether extracts of young bacterial cultures, 67 629-643
    - occurrence in chloroform extracts of young and older bacterial cultures, 67 828-852
    - occurrence in various bacterial extracts, 67 853-858
    - toxicity of, mechanism, 80 240-248
- Cord formation
  - relation to virulence, 78 83-92
  - titration, in acid-fast, wild-type, typical and atypical bacilli, (Notes) 78 799-801
- Cornea, tuberculosis, cortisone in, study with phase-contrast microscope, 74 1-6
- Coronary artery *See* Artery
- Coronary disease *See* Heart
- CORRESPONDENCE
  - absorption of shellac-coated PAS granules, with special reference to the age of the preparations, 76 159
  - acid-fast bacilli, nonpathogenic for guinea pigs, 74 478-480
  - acid-fast chromogens, frequency of, in gastric juice of nontuberculous patients, 79 543-544
  - aliphatic amines, effect on ability of virulent mycobacteria to bind neutral red, 60 384
  - allergy
    - exacerbation of pulmonary tuberculosis, 74 155-157
    - lethal allergic shock in experimental tuberculosis under streptomycin therapy, 75 343-344
  - ambulation of tuberculous patients under protection of chemotherapy, 71 602-603
  - antimicrobial therapy
    - in primary tuberculous infection in children, 72 398-402, 73 305
    - and prognosis of primary tuberculosis, 70 535
- BCG
  - fatal case of tuberculosis produced by, 71 321-323, 73 301-305
  - method of obtaining, 79 105
  - standardization, 65 641
  - Tice stain, 75 692-693

*Correspondence, BCG, cont*

- vaccination, 62 118-119
  - hyaluronidase effect on, 65 217-218
  - in Sweden, 79 678-679
- beryllium case registry at Massachusetts General Hospital, 72 129-132
- carbohydrate antibodies, precipitin test for, 59 710-712
- care of tuberculous in countries of limited means, 73 444-445
- chemotherapeutic activity
  - of streptomycin-PAS in experimental tuberculosis in mice, 60 808-810
  - of Triton WR 1339-macrocydon in murine leprosy, 76 915-916
- chemotherapy
  - for all active tuberculosis, 63 490-492
  - with eventual surgery in mind, for tuberculous patients, 74 476-478
  - in pneumoconiosis complicated by tuberculosis, 79 818
  - possibility of an antagonistic effect between pneumotherapy and, 70 533, 71 600-602, 766
  - to prevent relapse in patients with noninfectious tuberculosis, 80 108
  - prognosis of long-term, in tuberculosis, 70 178
- chlortetracycline in tuberculostatic activity, 59 221, 60 143
- chromogenic acid-fast bacilli from human sources, 72 693-694, 73 601-603
- coccidioidomycosis
  - contagiousness, 61 441
  - pulmonary, 61 158
- communion of mycobacteria by exposure to ultrasonics, 76 914-915
- concerning apical localization of postprimary pulmonary tuberculosis explained by the specific gravity of tuberculous material, 73 598-600
- DIAGNOSTIC STANDARDS—1950 edition, 63 721-722
- DIAGNOSTIC STANDARDS AND CLASSIFICATION OF TUBERCULOSIS, 1950, 74 158-159
- differential response to metabolites of *M. tuberculosis* H37Rv and H37Ra, 62 333
- diffuse interstitial pulmonary fibrosis and hypertrophic pulmonary osteoarthropathy, 79 513
- discharges from hospital, irregular, terminology for, 68 634-635, 73 597
  - fate of tuberculous patient and, 72 552-554
  - from tuberculosis sanatoriums, 70 755
  - in the U S A and Great Britain, 69 847-851
- effect of antihistamine medication on the tuberculin reaction, 60 811, 61 442
- effect of iodine on tuberculosis, 66 765-777
- enzymatic characteristics of suspensions of different mycobacteria, 61 270-271
- establishment of a beryllium case registry, 67 941-942
- filterable forms of *M. tuberculosis*, 69 473-474
- genitourinary transmission of tuberculosis, 75 153-155
- globulin titration technique, false positive reactions in, as applied to tuberculosis, 76 507-508
- hand talking chart, 70 534-535
- historic collection of pneumothorax machines and needles, 80 278
- importance of the social sciences for the control of tuberculosis in underdeveloped areas of the world, 75 345-346
- incidence of tuberculous infection in infancy, 74 808-809
- International Union Against Tuberculosis, 78 810
- iodine in leprosy, 68 295-296
- isoniazid
  - bacteriostatic action of, in presence of PABA, 76 706-707
  - chemoprophylaxis, in experimental tuberculosis, 74 475-476
  - clinical evaluation, 70 1102-1103
  - and coccidioidomycosis, pulmonary, 61 155
  - delirium, 69 845-846
  - diabetes affected by, 67 544
  - further observations on the correlation between serum concentrations and therapeutic response in human pulmonary tuberculosis, 80 108-110
  - indications for antituberculosis prophylaxis in the course of nontuberculous disease, 78 185
  - and mechanism of increasing bacteriotropic potencies of, in presence of PABA, 78 949-951
  - mode of action, 75 517-518
  - possible immediate deleterious effect on course of tuberculous meningitis, 71 765, 71 480
  - proposed mechanism of action for, in the tubercle bacillus and other biologic systems, 69 1062-1063
  - toxicity, 68 296-297
    - for the monkey, 68 470
  - used alone in the treatment of pulmonary tuberculosis, 70 924-925
- isoniazid C<sup>14</sup>, differential uptake by *M. para tuberculosis* susceptible and resistant to isoniazid-hydrogen peroxide, 80 110-111
- limitations of the guinea pig test, 70 371-77

*Correspondence, isoniazid, cont*

lung immobilizer therapy in pulmonary tuberculosis, 67 267

"mass X-ray" surveys, 60 532-535

mechanism of exacerbation in pulmonary tuberculosis with special reference to allergy, 71 155-157

mycobacteria, virulent

modified microcolonial test for, 73 600-601

*in vitro*, oxidation-reduction dyes for the determination of, 66 382-383

*M. tuberculosis*

possibility of sexual cycle, 63 721

relationship between *B. abortus* and, 71 478

*M. tuberculosis* H37Rv, 77 1031-1032

nucleinemia, 67 545-546

pancreas vs omentum in experimental tuberculosis, 80 445

pathogenesis and treatment of pulmonary tension cavities, 77 368

perils of procrastination in phthisiotherapy  
urgent indications for antituberculo-  
sis medication, 74 153-155

personnel pressure and the tuberculous patient, 76 912-914

plea for clearer distinction between allergic granulomatosis and Wegener's granulomatosis, 79 544-545

(on) Pinner's book, *Autobiographical Sketches of Disease by Physicians*, 63 492

pneumothorax induction, 69 844-845, 70 755

artificial, 72 252, 694

methods, 70 373-374

traumatic, 70 536-537

problem of the so called "good chronic" case of tuberculosis, 66 381

problems in laboratory diagnosis of tuberculosis, 76 1110-1111

proper designation of ammonium sulfate PPD, 74 810-811

proposal for reducing cost of care of the tuberculous in countries of limited means, 73 444-445

psychiatric evaluation of the personality of the tuberculous patient, 74 807

pulmonary tuberculosis during long-term single-drug (isoniazid) therapy, 71 314-315

rehabilitation and occupational therapy in tuberculosis hospitals, 79 680, 80 445-447

rehabilitation of tuberculous patients, 80 111-112

relationship of mycobacteria and mammalian cells in tissue cultures, 75 347-348

request for data on effects of cortisone and ACTH on tuberculosis in humans, 64 471-472

request for reprints concerning stress and the adaptive hormones, 67 677-678

resistance of a tuberculin reactor, 69 846-847

sarcoidosis, 75 852-854

failure to develop, after oral ingestion of pine pollen, 80 760

finding of lupus erythematosus cells in, 74 811

sensitivity to histoplasmin, 61 269

serum gamma globulins in pulmonary tuberculosis, 61 893-894

sophistry in use of the word "minimal," 79 681

source of scotochromogens, 80 277-278

sputum collection during local anesthesia, 75 854-855

"sputum conversion" and the metabolism of isoniazid, 77 869-871

streptomycin-isoniazid resistance, 75 346-347

surgical vs nonsurgical treatment of "open-negative" syndrome, 76 508-509

surgical reporting, 79 679-680

survival of bacilli in tuberculous lesions, 66 381-382

technique of drug-resistance tests, 70 922-923

terminology used for discharges from hospital, 80 447-448

test for PAS ingestion, 74 810

torsion of the spleen associated with pneumoperitoneum, 70 923

treatment

of active pulmonary tuberculosis outside institution, 76 506-507

failures, 79 105

of a recent tuberculin reactor, 69 843-844

of tuberculous lymphadenitis with sodium salicylate, 68 940-941

tubercle bacilli

counting chambers for enumeration of, 70 376-377

culture of, in test tubes or bottles, 77 1030

growth of, in monocytes from normal and vaccinated rabbits, 69 1059-1060

growth requirements

isoniazid-resistant, 75 155-156

virulence of, 69 640-641, 70 370-372

isolation, rapid microculture method for, 76 159-160

methanol extracts, 74 807-808

procedure for negative cultures of, 68 470-471, 69 128

simple device for microculture in blood, in pathologic specimens, 73 785-786

streptomycin-resistant, transmission of, 62 227

treated with isoniazid, virulence of, 69 641-644

viable and stainable counts, in tuberculous tissue, 75 519-520

*Correspondence, tubercle bacilli, cont*

- tuberculomas of the mediastinum, 65 215-217
- tuberculosis
  - fashionable in 1759, 80 110
  - "minimal," sophistry in use of word, 79 681
  - in South America, 67 676-677
  - tuberculin-negative, 64 168-171
  - vocational rehabilitation in, 79 513
  - tuberculous meningitis, 78 485
    - during isoniazid therapy, 74 480
  - vitamin A metabolism in tuberculous patients, 73 603-604
- Corticosteroids *See* Hormones
- Corticotropin *See* Hormones
- Cortisone *See* Hormones
- Cranium, calcification in, after serous tuberculous meningitis, (case reports) 78 101-105
- Cryptococcosis *See* Mycoses
- Cryptococcus neoformans* *See* Fungi
- Culture(s)
  - media, vs guinea pig inoculation, (Notes) 72 687-689
- of *M. tuberculosis*
  - in BCG-vaccinated mice, 79 484-491
  - chamber method technique, (Notes) 72 393-397
  - choice and standardization in experimental tuberculosis, 60 90-108
  - compared with mouse and guinea pig inoculation, 69 92-103
  - fibrin-clot technique for isolation of tubercle bacilli from pleural exudates, (Notes) 80 438-440
  - filter paper method, (Notes) 70 916-919
  - by incubation beyond normal 7- or 8 week period, (Notes) 69 307-308
  - new method for, (Notes) 69 304-306
  - purified tuberculin fraction from, (Notes) 69 300-303
  - from resected lesions, late emergence of, 70 191-218
  - slide method, 72 330-339
    - in detection of drug-resistant tubercle bacilli, (Notes) 75 331-337
    - in detection of *M. tuberculosis*, 60 51-61
    - for streptomycin testing, (correspondence) 59 599
  - from sputum
    - and gastric washings, trisodium phosphate transport digestion method of processing specimens, (Notes) 70 363-366
    - of isoniazid-treated patients, 70 349-359
    - with tracheal lavage, in diagnosis of pulmonary tuberculosis, 60 634-638
    - of tubercle bacilli, diagnostic media for, 63 459-469, 470-475
- Cyanacetic acid hydrazide, antituberculosis value of, 74 417-427
- Cycloserine
  - alone and in combination with other drugs in experimental tuberculosis, (Notes) 75 510-513
  - antituberculosis activity *in vitro* and *in vivo*, 73 539-546
  - ATS statement by Committee on Therapy, 75 1016-1017
  - clinical, bacteriologic, and pharmacologic observations on, (Notes) 74 128-135
  - disposition in humans, 74 739-746
  - effect on tubercle bacilli, 72 685-686
  - in experimental animals, (Notes) 74 802-806
- isoniazid
  - in ambulant tuberculosis therapy, (Notes) 80 89-94
  - in tuberculosis, pulmonary, (Notes) 79 87-88
    - high dosage, (Notes) 80 269-273
    - with other drugs, 75 553-575
- pyrazinamide, in pulmonary tuberculosis, (Notes) 78 927-931
- toxicity, 74 196-209, (Notes) 75 514-516
  - and pharmacology, (Notes) 74 972-976
- in tuberculosis
  - experimental, (Notes) 72 117, 856-858
  - human, (Notes) 74 121-127
  - pulmonary, (Notes) 76 1097-1099
    - psychologic effects, (Notes) 73 438-441
- viomycin, in pulmonary tuberculosis, (Notes) 79 90-93
- in vitro* action on *M. tuberculosis*, (Notes) 72 236-241
- Cystic disease, bronchogenic, with choleraesuis and *Aspergillus* infestation, (case reports) 74 92-98
- Cystoscopes, sterilization, (Notes) 76 909-911
- Cyst(s)
  - intrathoracic, after oleothorax, (case reports) 66 601-604
  - of lung *See* Cysts, pulmonary
  - primary mediastinal, and neoplasms in children, 74 940-953
  - pulmonary, 75 53-61
    - infected by *M. tuberculosis*, (case reports) 69 1037-1041
    - surgical management of, (case reports) 63 579-586
  - vascular anomalies associated with, (case reports) 71 573-583
- Cytology, in diagnosis of pulmonary malignancy, 61 60-65



Cytolysis test, of leukocytes  
 "plasma factor" in, (Notes) 79 211-215  
*in vitro*

in sarcoidosis, 63 672-673

by tuberculin, 60 212-222

Cytotoxicity of tuberculin, *in vitro*, failure to demonstrate for the cells of sensitized animals, 63 674-678

## D

Deborah Sanatorium and Hospital (Philadelphia, Pennsylvania), international symposium, November 20-22, 1958, 80 (Supplement, October 1-139)

Decontamination of articles made by tuberculous patients, Carboxide<sup>®</sup> gas for, 72 272-279

Decortication of lung

pulmonary function after, 63 231-251

bronchspirometric study, 66 509-521

in pulmonary tuberculosis, 59 30-38, 60 288-301

Deformities, prevention of, after thoracoplasty, 66 436-448

Desoxyribonucleic acid

failure to induce bacterial transformation, (Notes) 80 911

as growth stimulant of tubercle bacilli, 80 866-870

Detention ward, in tuberculosis treatment and control, 74 410-416

Diabetes

alloxan-induced, in albino rats, 65 603-611

insipidus, pulmonary histiocytosis with, (case reports) 79 652-658

isoniazid effect on, (correspondence) 67 544

and tuberculosis, 65 (Supplement, January 1-50), 76 1016-1030, 77 990-998

surgery for, 74 747-755

Diagnosis

by auscultation, 60 639-647

bacteriologic, 59 589-598

differential

bronchogenic carcinoma as a problem of, in pulmonary disease, 63 176-193

of pulmonary lesions, importance of tuberculin test in, 63 140-149

of pulmonary tuberculosis, tracheal lavage and culture in, 60 634-638

DIAGNOSTIC STANDARDS AND CLASSIFICATION OF TUBERCULOSIS of the National Tuberculosis Association

1950 edition, (correspondence) 63 721-722

history of, 65 494

4 4'-Diaminodiphenyl sulfone, excretion products, (Notes) 72 123-125

Diaphragm

pneumocoele in, complicating therapeutic pneumoperitoneum, 69 745-759

rupture of

complicating pneumoperitoneum, resulting in spontaneous pneumothorax, (case reports) 63 587-590

during pneumoperitoneum, (case reports) 60 794-800

Diatomaceous earth, pneumoconiosis and, 77 644-661

Diet(s)

controlled, urinary excretion in, 69 439-454

effect on resistance by viable and nonviable vaccines, 77 93-105

Differential diagnosis See Diagnosis

Diffusing capacity for oxygen during exercise, 80 806-821

Dihydrostreptomycin

in avian tuberculosis in chicks, comparison with streptomycin, 60 366-376

-corticotropin, in experimental bovine tuberculosis in rabbit, 67 201-211

-cortisone, in experimental tuberculosis in guinea pig, (Notes) 67 101-102

neurotoxicity, effects of longer-term therapy, 63 312-324

-PAS, in experimental tuberculosis in guinea pigs, 62 149-155

purified, (Notes) 73 776-778

resistance, genetic studies of, in *M. ranac*, 62 286-299

sulfate, in pulmonary tuberculosis, neurotoxicity of, 65 612-616

toxicity, 60 564-575

-Triton A-20 in experimental tuberculosis in mice, 65 718-721

tubercle bacilli, dihydrostreptomycin-resistant strains, enhancement of growth by, a function of initial pH value of the medium, 63 568-578

in tuberculosis

experimental, in guinea pigs, effect of in combination with Tibione<sup>®</sup> as compared when combined with PAS, 63 339-345

pulmonary, 62 572-581

compared with streptomycin, 68 229-237, 238-248

in tuberculous empyema, drug concentrations attained with various vehicles, 66 271-284

cellugel as vehicle, 66 285-291

3,5-Duodo-4 pyridone N-acetic acid in bronchography, 74 178-187, 188-195, 77 32-38

effect on blood iodine, (Notes) 77 181-183

- 1,4-Dimethyl-8-isopropyl-bicyclo-decapentane-Triton A-20, therapeutic activity in experimental tuberculosis and leprosy, (Notes) 75 684-687
- Dionosil® See 3,5-Duodo-4 pyridone N-acetic acid
- Discharge(s) (from hospital)
- irregular, of tuberculous patients, 66 213-216, 68 393-399, (correspondence) 69 634-635, (correspondence) 70 755, 71 419-428, (correspondence) 72 552-554, (correspondence) 73 597
  - problem of, (editorials) 70 892-898
  - scale for predicting, 73 338-350
  - special ward procedure, 72 633-646
  - in the U S A and Great Britain, (correspondence) 69 847-851
  - terminology, (correspondence) 80 447-449
- Discriminant analysis, in prediction of relapse in pulmonary tuberculosis, 73 472-484
- Disease, chronic, time factor in studies of the outcome, (editorials) 63 608-612
- Dispersion, in relation to virulence of tubercle bacilli, 75 488-494
- Dissemination of tubercle bacilli in experimental tuberculosis in guinea pigs, 61 399-406
- Diverticula, traction, of esophagus in middle lobe syndrome, 65 455-464
- DL-Serine, toxic effects on virulent human tubercle bacilli, (correspondence) 60 385
- Dogs, amithozone toxicity in, 64 659-668
- isoniazid-ipromiazid effect on central nervous system in, 69 261-266
- tuberculosis in
- bronchogenic, 73 748-763
  - experimental, 61 77-94
  - treated with isoniazid, 65 376-391, 392-401
- Douglas bag, in maximal breathing capacity with spirometry, (Notes) 79 253-255
- Drainage
- closed, and thoracoplasty in tuberculous empyema, 66 522-533
  - following pulmonary resection, (Notes) 69 636-637
  - lymphatic, of pleural space in dogs studied with radioactive gold (AU<sup>198</sup>), (Notes) 75 145-147
  - surgical, of emphysematous bulla, (case reports) 61 742-746
- Drug(s) See also Antimicrobials, Chemotherapy, and specific drugs
- ancillary, in resection of drug-resistant cavitary tuberculosis, 79 780-789
- antituberculosis
- roentgenography as index of effect of, 68 65-74
  - screening of, in guinea pigs, 68 48-64
  - therapy with paired combinations of, 80 627-640
  - in tuberculosis, (Notes) 78 121-126
- fever, due to isoniazid, (case reports) 68 249-252
- new, in tuberculosis, scientific appraisal of, (editorials) 61 751-756
- resistance
- in pulmonary resections, 75 781-792
  - tests (correspondence), 70 922-923
- susceptibility tests, *in vitro*, with *M tuberculosis*, 63 679-693
- therapy
- preresection, in pulmonary tuberculosis, 79 41-46
  - in tuberculosis, (Notes) 74 968-971
- Dubos medium See Medium(a)
- Dubos-Middlebrook hemagglutination test See Hemagglutination
- Duck embryos, mycobacteria in, 73 276-290
- Duodenum, rupture, with arteritis of abdominal aorta, (case reports) 60 801-807
- Dusts See also Pneumoconioses
- Fiberglas®-plastic, and tuberculosis, 78 512-523
- Dyes, oxidation-reduction, in determination of virulence of mycobacteria *in vitro*, 65 187-193
- Dyspnea
- in beryllium workers, 59 364-390
  - in Parkinson's syndrome, 78 682-691
- ## E
- Eating utensils, tuberculous contamination of, (Notes) 74 462-463
- ## EDITORIALS
- air pollution and bronchitis, 80 582-584
- antihistamines and the tuberculin reaction, 62 555
- acceleration of tuberculosis research, 71 140-143
- BCG vaccine
- immunologic aspects, 60 670-674
  - progress toward standardization of, 79 80-82
- changes ahead for the American Trudeau Society, 75 648-649
- chemoprophylaxis, immunity, and prevention in tuberculosis, 74 117-120
- closing of the Trudeau Sanatorium, 71 163-164
- cooperative clinical research in tuberculosis, 68 263
- cost of tuberculosis research, 60 527-531
- creative spirit in research, 64 113-116
- effect of isoniazid on the program of the tuberculosis association, 66 615-620
- emotional problems in the treatment of tuberculosis, 71 299-301

*Editorials, cont*

- fiftieth anniversary of the National Tuberculosis Association, 69 631-633
- hemagglutination test in tuberculosis, 62 223-226
- on history repeating itself, 74 793-795
- implications of the phenomenon of "open cavity" healing for the chemotherapy of pulmonary tuberculosis, 71 441-446
- implications of rapidly effective tuberculosis therapy, 61 892
- integration of streptomycin with other forms of therapy for pulmonary tuberculosis, 50 264-268
- limitations of knowledge about para-aminosalicylic acid, 76 491-496
- lymph node tuberculosis and its treatment in accessible nodes, 64 691-694
- mass roentgenographic surveys in small hospitals, 64 313-317
- natural healing and chemotherapy, 76 669-670
- natural history of tuberculosis in the human body, 80 100-107
- necessity for accurate evaluation of the results of thoracoplasty, 60 383
- philosophy of abstracting, 62 446-448
- place of the laboratory in the tuberculosis sanatorium, 73 291-293
- pneumothorax induction by lung puncture or "orthodox" technique, 69 121-124
- problems
  - of immunity in nontuberculous infections, 71 592-595
  - of irregular discharge, 70 892-898
  - of tuberculosis in psychotics, 68 782-785
- psychologic aspects of tuberculosis, 67 869-873
- relationship(s)
  - of the immunity mechanism to pathologic changes, clinical symptoms, and therapeutic measures in tuberculosis, 68 933-937
  - of tuberculous infection to illness, 71 885-888
- scientific appraisalment of new drugs in tuberculosis, 61 751-756
- share in the task ahead, 67 517-521
- specific therapy for tuberculous meningitis, 61 263-268
- specificity of the tuberculin reaction, 63 355-359
- standardization and stability of purified tuberculin, 80 255-256
- thirty years of tuberculosis therapy in a municipal sanatorium, 70 518-520
- time factor in studies of the outcome of chronic disease, 63 608-612
- treatment
  - of female genital tuberculosis, 75 501-505
  - by inhalation, 74 454-456
  - tuberculosis
    - as a cause of female sterility, 70 1096-1098
    - in medical teaching, 60 140-142
    - on the Navajo reservation, 61 586-591
  - tuberculous alcoholic before and during hospitalization, 79 659-662
  - vocational rehabilitation in pulmonary tuberculosis today, 78 647-649
  - United States Public Health Service cooperative clinical investigation of bacterial resistance, 70 739-742
  - World Health Organization and tuberculosis, aims, objects, and accomplishments, 64 218-222
  - understanding of personality patterns as guide for rehabilitation of the tuberculous, 65 481-483
- Education for tuberculous patients, 70 490-497
- Effusion(s)
  - peritoneal, complicating pneumoperitoneum, (case reports) 66 90-94
- pleural
  - biopsy, 78 8-16
  - idiopathic, 72 647-652
  - thoracotomy in, 74 954-957
  - pathology, 71 473-502
  - primary, 59 259-269
  - serofibrinous, in military personnel, 71 616-634
- proteins and mucoproteins, 76 247-255
- tuberculous, 62 314-323
  - age distribution of, (Notes) 70 901-902
  - in children, 77 271-289
  - modified bed rest in, 67 421-431
  - prednisone in, 79 307-314
- Egg(s)
  - albumin, in production of nontuberculous cavities in experimental tuberculosis, 75 99-104
- embryo
  - in rapid detection of tubercle bacillus, (Notes) 76 315-320
  - isolation of *M. tuberculosis* on, (Notes) 70 912-915
- yolk media
  - in isolation of *M. tuberculosis*, (Notes) 72 863-865
  - for tubercle bacilli, 70 977-988
- Elastin, of lung, 80 (Supplement, July 45-48)
- Electrocardiography
  - changes in
    - after chest surgery, 59 128-139
    - after mediastinal shift, 64 64-70
    - after pulmonary collapse and surgery, 64 50-63
  - in pneumoperitoneum, 61 335-345
  - with prominent S waves, 62 307-313
  - in pulmonary tuberculosis, surgically treated, 65 443-450

- Electro-encephalogram, isoniazid effect on, 70 476-482
- Electron microscopy *See* Microscopy
- Electrophoresis
- effect of cortisone, and the hemagglutination reaction in childhood tuberculosis, 73 964-965
  - in study of serum proteins in tuberculosis, 68 372-381, (Notes) 75 999-1002, (Notes) 76 892-895, (Notes) 79 522-524
  - zone, in starch gels, report on Smithies method in normal adults and in patients with tuberculosis, 78 932-933
- Embolism
- air
    - in pneumoperitoneum, 69 396-405
    - millwheel murmur presumably caused by, (case reports) 70 1092-1095
- Embolus, experimental, localization of, 70 557-569
- Embryo, chick, efficacy as medium for isolating tubercle bacilli, (Notes) 76 703-705
- Emotions of tuberculous patients, effect of isoniazid on, 68 523-534, 70 476-482
- Emphysema
- air-flow physics in, 80 (Supplement, July 123-125)
  - allergy in, 80 (Supplement, July 181-183)
  - alveolar, chronic, in horse ("heaves"), 80 (Supplement, July 141-143)
  - bullous
    - bilateral, pulmonary function tests in, (case reports) 71 867-876
    - after resection, 77 387-399
  - and "chronic bronchitis" syndrome, symposium on (Aspen, Colorado, June 13-15, 1958), 80 (Supplement, July 1-213)
  - clinical aspects, 80 (Supplement, July 169-171)
  - conference, summary of, 80 (Supplement, July 209-212)
  - definition, 80 (Supplement, July 114)
  - diagnosis, physical and roentgenographic signs and oximeter test in, 80 705-715
  - diffuse, obstructive, surgery in, 80 825-832
  - experimental
    - in guinea pig, 80 (Supplement, July 147-151, 153-154)
  - familial, 80 (Supplement, July 179-180)
  - longitudinal studies in, (Notes) 80 915-918
  - macrosection and injection studies of, 80 (Supplement, July 94-103)
  - in man, natural history of, 80 (Supplement, July 169-171)
  - mediastinal
    - complicating pneumoperitoneum induction, (case reports) 63 591-596, 68 775-781
    - therapeutic, (Notes) 76 897-898
  - spontaneous, and bilateral spontaneous pneumothoraces, 61 883-886
  - microradiography, 80 (Supplement, July 104-112)
- obstructive
- chronic, cardiopulmonary function in, 80 689-699
  - chronic bronchitis as etiologic factor, 80 (Supplement, July 185-193)
  - corticotropin-cortisone in, 64 279-294
  - pathogenesis, theories of, 80 (Supplement, July 2-4)
  - pathology, 80 (Supplement, July 58-64)
  - pulmonary
    - chronic, 69 915-929
    - basic lesion in, 68 24-30
    - breathing, energy cost and control of, 80 (Supplement, July 131)
    - pathogenesis, 62 45-57
    - respirators in, 80 510-521
    - ventilation in, 74 210-219, 220-228
  - circulatory dynamics, during treadmill exercise, 80 (Supplement, July 128)
  - in coal miners, 59 270-288
  - diffusion in, 71 249-259
  - early, 72 569-576
  - experimental, 78 848-861, 80 (Supplement, July 158-167)
  - hypoxia due to, hematologic adaptation in, 78 391-398
  - lymphatics in reference to, 80 (Supplement, July 50-56)
  - obstructive, chronic
    - chemoprophylaxis in, 80 716-723
    - cigarette effects in, 76 22-32
  - and peptic ulcer, 80 (Supplement, July 155-156)
  - severe, intermittent positive pressure breathing in, 76 33-46
  - surgery in, 80 (Supplement, July 194-202)
  - variability of behavior within, 80 (Supplement, July 136)
  - and vascular changes, 80 (Supplement, July 67-91)
  - registry for, 80 (Supplement, July 207-208)
  - unusual forms, 80 (Supplement, July 172-178)
  - ventilation mechanics in, 80 (Supplement, July 118-120)
- Emphysematous bulla *See* Bulla
- Empyema
- in pulmonary tuberculosis, 59 601-618, 78 411-425
- tuberculous
- alkalinization in, 66 271-284, 285-291
  - clinical course and management, 61 662-677
  - closed drainage and thoracoplasty in, 66 522-533
  - pH of, (Notes) 67 103-105

*Empyema, tuberculous, cont*

- streptomycin and dihydrostreptomycin in drug concentrations attained with various vehicles, 66 271-284
    - cellugel as vehicle, 66 285-291
  - Endobronchitis, tuberculous, occult, in surgical lung specimens, 77 931-939
  - Endothelioma *See* Tumors
  - Enterocolitis tuberculous
    - acute, obstructive, treated by nonsurgical ileostomy and streptomycin, (case reports) 60 648-653
    - streptomycin in, 60 576-588
  - Enumeration technique for viable tubercle bacilli, 76 616-635
  - Enzyme(s)
    - to aid filtration of oropharyngeal washes, (Notes) 79 541
    - digestion of, in separation of *M leprae* from tissues, (Notes) 74 152
    - in meningitis, 71 12-29
    - parenterally administered, in lung abscess, 76 1-21
    - purine, in mycobacteria, (Notes) 66 240-243
    - serum, in pulmonary tuberculosis, (Notes) 79 251-252
    - of tubercle bacillus, reactions of, and the action of streptomycin, 65 722-734
    - in tuberculosis, extrapulmonary, suppurative, 71 1-11
  - Eosinophilia
    - Löffler's syndrome, (case reports) 63 480-486
    - during PAS therapy, (case reports) 70 171-175
    - with pulmonary infiltration, 59 679-686
    - and pulmonary malignancy, (case reports) 75 644-647
  - Epidemiology
    - sarcoidosis with special reference to, 62 403-407
    - of tuberculosis, 67 123-131, 68 1-8, 75 432-441
  - Epilepsy, isoniazid therapy in, hazards, (case reports) 66 501
  - Epinephrine, as bronchodilator agent, 77 729-736
  - Erie County (New York), tuberculosis case-finding program, 59 78-85
  - Erythema
    - induratum (Bazin), with tuberculous lymphadenitis, (case reports) 60 249-257
    - nodosum with tuberculin-neutralizing serum, (case reports) 62 112-115
  - Erythrocyte(s)
    - OT-sensitized sheep, and trypsinized human, serologic relation of, 79 622-630
    - sedimentation rate, in pulmonary tuberculosis, 69 595-598
    - tuberculin-treated, as antigen in eliciting cutaneous hypersensitivity to tuberculin, (Notes) 64 322-326
  - Erythromycin, in chemoprophylaxis of empysema, 80 716-723
  - Esophageal inflation of hernial sac during pneumoperitoneum, (case reports) 75 823-827
  - Esophagobronchial fistula *See* Fistulas
  - Esophagocutaneous fistula *See* Fistulas
  - Esophagus, traction diverticula of, in middle lobe syndrome, 65 455-464
  - Estrogen(s)
    - effect
      - on progress of tuberculosis, 59 198-218
      - on tuberculin skin sensitivity and on allergy of internal tissues, 59 186-197
      - on tuberculosis in rabbits, 59 168-185
  - Ethionamide *See* Alpha-ethyl-thioisonicotinamide
  - (S)-Ethyl-L-cysteine, 70 806-811
    - effect of ventilation on antituberculosis activity of, 74 68-71
    - in pulmonary tuberculosis, (Notes) 74 142-144
  - Ethyl mercaptan, antituberculosis activity of, 74 72-77
  - Ethyl-thio formyl compound, antituberculosis activity of, (Notes) 77 1017-1018
  - Europe, rehabilitation of tuberculous patients, 66 104-108
  - Eventration, transdiaphragmatic, in pneumoperitoneum, (case reports) 69 1045-1050
  - Exacerbations, post-thoracoplasty, 61 648-661
  - Excision, surgical, and lobectomy in esophago-bronchial fistula, (case reports) 63 220-226
  - Exercise, and rest, in minimal pulmonary tuberculosis, 69 50-57
  - Expiratory force, index of, in ventilatory capacity tests, 78 692-696
  - Exudate, pleural, fibrin clot culture technique for isolation of tubercle bacilli from, (Notes) 80 438-440
  - Eye, tuberculosis of
    - cortisone in, study with phase contrast microscope, 74 1-6
    - in rabbits, 64 197-206, 207-217
- F**
- Fenestration, tracheal, evolution and early results of, 79 773-779
  - Fiberglas®-plastic dust and tuberculosis, 78 512-523
  - Fibrin bodies, simulating "coin lesions," (case reports) 72 659-662
  - Fibrin-clot culture technique for isolation of tubercle bacilli from pleural exudates, (Notes) 80 438-440

- Fibrosis**  
 pulmonary  
   and bronchiolar carcinoma, 76 559-567  
   carbon monoxide diffusing capacity in, 74 317-342  
   cardiopulmonary function in, 80 700-704  
   interstitial  
     diffuse, (case reports) 68 603-614, 74 485-510  
     Hamman-Rich syndrome, (case reports) 78 610-622  
     and hypertrophic osteoarthropathy, (correspondence), 79 543
- Fibrothorax**, tuberculous, angiopneumography and bronchography in, 73 61-71
- Filter membrane**  
   for tuberculous sputum, (Notes) 77 1019-1022  
   used in detection of tubercle bacilli in mouth wash, 71 371-381
- Fistula(s)**  
   esophagobronchial  
     associated with severe hemorrhage treated by surgical excision and lobectomy, (case reports) 63 220-226  
     in mediastinal tuberculosis, (case reports) 79 238-243  
   esophagocutaneous, treated with streptomycin and gastrostomy, 59 687-691  
   tuberculous, isoniazid-PAS in, 68 535-540
- Fitzsimons Army Hospital** (Denver, Colorado), tuberculin reaction in tuberculous patients, 80 569-574
- Fluorescence microscopy**  
   in detection of mycobacteria in tissue sections, 68 82-95  
   of *M. tuberculosis*, 65 709-717
- Foci**, round, tuberculous, 73 805-817
- Food intake**  
   in nontuberculous patients receiving isoniazid, 68 207-211  
   of tuberculous women, 60 455-465
- Formosa** (Taiwan), tuberculosis in, 80 359-370
- Freezing**, for preservation of stock cultures of *M. tuberculosis*, 62 99-100
- Friedlander's pneumonia**, 61 465-473
- Fume fixation of lung**, 79 764-772
- Functional residual capacity**, methods of measurement, 74 729-738
- Fungal antigens**  
   coccidioidin  
     sensitivity  
       with pulmonary calcifications, 59 643-649  
       on the Isthmus of Panama, 63 657-666  
     skin reaction in pulmonary coccidioidomycosis, (case reports) 79 78-79  
   histoplasmin  
     conversion rates in Kansas City as indication of prevalence of infection, 69 234-240  
     skin tests, effect on skin reactivity and colloid agglutination, 66 588-593  
     sensitivity to, (correspondence) 61 269  
       in Alaskan natives, (Notes) 79 542  
       in chronic pulmonary disease, 72 274-296  
       with pulmonary calcifications, 59 643-649  
       with pulmonary infiltration, 59 636-642  
       in young school children, 78 667-681  
       urban focus of, (Notes) 79 83-86  
   histoplasmin H-42, for skin testing, (Notes) 77 546-550  
     sensitivity to, in students, 73 620-636
- Fungal disease** See Mycoses
- Fungus**(s) See also Mycoses  
   Actinomycetales  
     cultural differentiation, 76 770-788  
     isoniazid susceptibility compared with other synthetic and antimicrobial antituberculosis agents, (Notes) 67 261-264
- Allescheria boydii*  
   fatal pulmonary infection with, (case reports) 78 604-609  
   in sputum, (case reports) 71 126-130
- Aspergillus fumigatus*, significance in sputum, 80 167-180
- Aspergillus* infestation, with cystic disease, (case reports) 74 92-98
- Blastomyces dermatitidis* as antigen for polysaccharide skin test, 77 983-989  
   and *Histoplasma capsulatum*, polysaccharide skin tests on humans, (Notes) 80 264-266
- Candida albicans*  
   and adjuvants, sensitization of guinea pigs, (Notes) 76 692-696  
   detection, on culture media of *M. tuberculosis*, 75 836-840  
   in tuberculous sputum, (Notes) 77 543-545
- Coccidioides immitis*  
   hyphae of, in human tissues, 70 320-327  
   immunization against, 74 245-248  
     experimental, 70 498-503  
   isoniazid-isoniazid effect, (Notes) 67 538  
   sporulation inhibited by peptone, (Notes) 74 147-148
- Cryptococcus neoformans*, causing pulmonary lesion, 74 441-444
- Histoplasma capsulatum*  
   as antigen for polysaccharide skin test, 77 983-989  
   and *Blastomyces dermatitidis*, polysaccharide skin tests on humans, (Notes) 80 264-266  
   isolation from sputum, 66 578-587  
   laboratory infection, (Notes) 72 690-692  
   in *Macacus irus* monkeys, (Notes) 75 849-851

*Fungus(s), Histoplasma capsulatum, cont*

- pulmonary cavitation caused by, (case reports) 69 111-115
- reactions to, in rabbits, 62 371-389

*Nocardia*

- characterization of species, 76 151-479
- cultural differentiation, 76 770-788

*Nocardia asteroides*, PPD and other antigens prepared from, 79 284-295

- pathogenic, and yeasts, culture filtrates of, tuberculostatic properties of, (Notes) 66 623-625

- in pulmonary diseases in India, (Notes) 78 644-646

**G***Gamma globulin*

- in childhood tuberculosis, 74 15-28
- content of serum in pulmonary tuberculosis, (correspondence) 61 893-894

*Gas See also Pulmonary function**exchange*

- and pulmonary circulation, influence of ventilatory mechanics on, 80 53-58
- and respiratory ventilation in chronic pulmonary emphysema, mechanical respirators in, 80 510-521
- intrapulmonary, mixing after lobectomy, 78 1-7
- mixing in tuberculous lung, 74 343-350
- in tuberculous cavities, 80 1-5

*Gastric aspiration for culture of M tuberculosis*, 67 598-603*Gastric dilatation after phrenic nerve interruption*, (case reports) 62 331-332*Gastric lavage*

- culture for *M tuberculosis*, trisodium phosphate transport-digestion method of processing specimens, (Notes) 70 363-366
- and laryngeal swabs in isolation of tubercle bacilli, 73 930-939
- method of obtaining, 60 228-235
- pancreatin-quaternary ammonium treatment, 74 616-621

- for tubercle bacilli, evaluation of four methods of collecting and mailing, 65 617-626

*Gastric tuberculosis See Tuberculosis, gastric**Gastric washings See Gastric lavage**Gastrointestinal changes in pneumoperitoneum*, 66 750-757*Gastrostomy, in esophagocutaneous fistula*, 59 687-691*Gelatin foam, in thoracoplasties*, 61 193-200*Gel-diffusion techniques*

- precipitation, in tuberculosis, 77 450-461
- with tuberculin antigens, 75 601-607

*tests for tuberculosis*, 80 886-894*double-*, 80 152-166*Genetic resistance to tuberculosis in rabbits*, 72 297-329*Genitourinary tuberculosis See Tuberculosis, genitourinary**Georgia**compulsory isolation of tuberculous patients*, (Notes) 77 506-510*tuberculosis studies in Muscogee County*, 73 157-164*Geotrichosis See Mycoses**Germany, tuberculosis in*, 59 481-493*Globulin titration*

- in demonstration of circulating antibodies after BCG immunization, (Notes) 78 793
- technique in tuberculosis, (correspondence) 76 507-508

*Glucose**effect on tuberculin reaction in tissue culture*, 78 712-724*metabolized by M smegmatis*, (Notes) 73 589-592*and oxygen, in autolysis of M tuberculosis*, 73 907-916*transfer of, into cerebrospinal fluid in tuberculous meningitis*, 67 732-754*Glucosulfone activity on H37Rv strain of M tuberculosis*, 59 461-465*D-Glucuronolactone isonicotinyl hydrazide-isoniazid, inhibitory activity*, 73 892-906*Glutamic acid, affect on mycobacteria*, (Notes) 75 688-691*Glutamic ovalacetic transaminase, in pulmonary tuberculosis*, (Notes) 79 251-252*Glutamic pyruvic transaminase, in pulmonary tuberculosis*, (Notes) 79 251-252*Glycerol**containing zinc*, (Notes) 74 145-146*effect on growth of M tuberculosis*, 74 50-58*Glycoprotein of serum in tuberculous guinea pigs*, 68 594-602*Goiter following PAS therapy*, (case reports) 69 458-463*Gold (Au<sup>199</sup>)**radioactive, for determining lymphatic draining of pericardium*, (Notes) 76 906-908*in study of lymphatic drainage in dogs*, (Notes) 75 145-147*Gold miners, silicotic, lung function in*, 77 400-412  
(See also Pulmonary function)*Gonadotropin**chorionic, effect on tuberculosis in rabbits*, 59 168-185*effect on progress of tuberculosis*, 59 198-218*Grafts, bone, homogenous, ribs from thoracoplasty as possible source of*, 63 210-212

Granulocytes in attempt to transfer tuberculin  
type of sensitivity, 64 516-519

Granuloma, coccidioidal *See* Mycoses and Tumors

Granulomatosis *See also* Pneumoconioses and Wegener's granuloma  
allergic, and Wegener's, distinction between,  
(correspondence) 79 544-545  
pathergic, of lungs, 78 21-37

Great Britain, irregular discharge in, (correspondence) 69 847-851

Guillain-Barré syndrome after PAS, (case reports) 69 455-457

Guinea pig(s) *See also* Tuberculosis, experimental

4-acetylaminobenzal thiosemicarbazone (Tibione) in tuberculosis of, 62 144-155

BCG infection, cortisone in, 69 511-519

BCG vaccine and hyaluronidase in, 68 188-198

corticotropin-cortisone in, 64 295-306

cortisone in tuberculous lesions of, 62 337-344

in detection of tubercle bacilli  
compared with mice and artificial media, 69 92-103  
from dispersed cultures, 65 572-588

with discrete chronic tuberculous lesions, streptomycin in, 66 194-212

in experimental tuberculosis  
antituberculosis drug screening in, 68 48-64  
cortisone-dihydrostreptomycin in, (Notes) 67 101-102

dissemination of tubercle bacilli, 61 399-406

effect of dihydrostreptomycin-PAS on, 62 149-155

irradiated antituberculosis vaccine and BCG in, 67 341-353

isoniazid in, 68 75-81

neomycin in, 62 300-306, 345-352

serum glycoprotein in, 68 594-602

streptomycin in, 68 575-582

treated with isoniazid, 65 365-375, 376-391

treated with potassium iodide-streptomycin, 66 680-698

treated with pyrazinamide, 65 519-522

immunogenicity for, of BCG cultured in bile, 59 102-105

inoculation, for detection of tubercle bacilli, limitations of, (correspondence) 70 374-375

inoculation versus culture on artificial media, (Notes) 72 687-689

intradermal tuberculin reaction on, 69 806-817

omentum used as index in chemotherapy, 68 583-593

potassium iodide-streptomycin in, 64 102-112

sensitization, mycobacterial wax in, 69 241-246

streptomycin-PAS in intracerebral infection of, 64 87-101

tuberculous  
abortive tuberculosis induced in by pathologic material containing young tubercle bacilli, (correspondence) 68 467

pyrazinimide in, (Notes) 70 367-369

serum protein in, 70 344-348

thioureas, substituted in, 70 130-138

tuberculous meningitis in  
isoniazid, iproniazid, streptomycin, and streptomycin-isoniazid in, 70 714-727

produced by lumbar intrathecal inoculation, 66 722-731

virulence  
correlated with catalase activity and isoniazid resistance, (Notes) 72 246-251

of isoniazid-resistant cultures in, (Notes) 68 290-291

of isoniazid-resistant tubercle bacilli in, (Notes) 69 464-468

## H

Hamartoma *See* Tumors

Hamman-Rich syndrome, 74 485-510  
cortisone in, (case reports) 76 123-131  
pathogenesis of, 78 353-367  
report of three cases, (case reports) 78 610-622

Hand talking chart, (correspondence) 70 534-535

Hawai  
resection for pulmonary tuberculosis in, 80 6-11

tuberculosis in, 68 839-862

Heart  
atherosclerosis, (symposium) 71 904-924

block, change in tuberculosis of myocardium, (case reports) 65 332-338

disease, Beck operations for (symposium), 71 904-924

involvement in military tuberculosis, (case reports) 68 771-774

symptoms in tuberculosis, 62 (Supplement, July 98-103)

tuberculosis of, 62 390-402

"Heaves" *See* Emphysema, alveolar, chronic

HeLa cells *See* Cells

Helium-dilution method  
closed-circuit, in measuring functional residual capacity, 74 729-738

in ventilation study, 79 450-456

Hemagglutination  
procedure in study of tuberculins, 65 272-277

reaction  
after BCG, 66 58-62

antiglobulin modification of, 68 739-745

clinical evaluation of, 67 497-502

in tuberculosis  
in children, 70 139-148

diagnosis of, 64 71-76



*Hemagglutination test*

test

for antibodies, 65 191-200

and its hemolytic modification in tuberculosis, 65 191-200, 66 591-600

complement fixation modification (Mallard) of, in tuberculosis, (Notes) 66 621-622

Middlebrook Dubos, clinical interpretation, 62 121-127

modification of slide test for antibodies against tubercle bacilli, 63 667-671

in tuberculosis, (editorials) 62 223-226

Hemagglutinin adsorption, specificity of, in serologic study of tuberculosis, 67 657-664

Hemangiopericytoma *See* TumorsHemangiosarcomatosis *See* TumorsHematoma *See* Tumors

Hemidiaphragm, paralyzed, effect on homolateral thoracoplasty, 60 183-188

*Hemin*

antagonism of isoniazid, (Notes) 69 469-470

as growth factor in isoniazid resistant strains of *M. tuberculosis*, 69 797-805

Hemoglobin, and methemoglobin, values in tuberculous patients on isoniazid therapy, (Notes) 68 286-289

Hemolytic and hemagglutination tests in tuberculosis, 66 591-600

Hemopneumothorax, spontaneous, 62 513-518, (case reports) 65 711-753

benign, 63 417-426

surgery for, 71 30-48

Hemoptysis, in chest clinic patients, 63 191-201

*Hemorrhage(s)*

in emphysematous bulla, (case reports) 61 742-746

intraperitoneal, occurring as a complication of pneumoperitoneum, 63 116-118

fatal, in pulmonary tuberculosis, 60 589-603

pulmonary, in tuberculosis, (case reports) 62 321-330

pneumonectomy for, (case reports) 61 426-430

*Hemothorax*

spontaneous, (case reports) 71 755-761

in therapeutic pneumothorax, (case reports) 50 654-659

*Hepatitis*

choleangiolitic, due to PAS, (case reports) 76 132-139

and hypokalemia in tuberculosis, (case reports) 68 136-143

post transfusion, with sickle cell anemia, (case reports) 67 247-257

pyrazinamide in, serum enzymes in, 80 855-865

pyrazinamide induced, (case reports) 77 858-862

Hepatolysis, in pneumoperitoneum, (case reports) 69 297-299

5 Heptyl 2 thiohydantoin in experimental tuberculosis, 78 71-82

*Hernia*

esophageal, hiatal, pneumoperitoneum in, (case reports) 78 623-631

inguinal, pneumoperitoneum in, (case reports) 60 521-526

Heterocyclic acid hydrazides *See* Acids*n* Hexadecane as adjuvant for BCG in mice, 75 621-629

Hi Intensity ultraviolet for sterilization, (Notes) 71 157-158

Hilum, triangular shadows of, 66 188-193

*Hinestarch*

antituberculous activity, 73 72-78

metabolic products, (Notes) 71 798-801

in pulmonary tuberculosis, 73 219-228, 77 952-967

seromucoid (serum mucoprotein) values, (Notes) 78 131-134

Histidine, utilization of, in production of a pharmacologically active metabolite, 63 100-107

Histiocytosis X, pulmonary, (case reports) 75 319-325

with diabetes insipidus, (case reports) 79 652-658

*Histoplasma capsulatum* *See* FungiHistoplasmin *See* Fungal antigensHistoplasmin H-42 *See* Fungal antigensHistoplasmosis *See* Mycoses

Home, and hospital, in tuberculosis, including chemotherapy of, 80 (Supplement, October 23-45)

Hong Kong, tuberculosis in, and BCG, 76 215-224

Honolulu schools, tuberculin testing in, 78 871-883

Hooke's law, application to elastance of lung, (Notes) 77 863-866

*Hormones(s)*

adaptive, request for reprints on stress and, (correspondence) 67 677-678

adrenal, in experimental ocular tuberculosis, 66 175-186

corticosteroids and corticotropin in tuberculosis, 76 708-710

*corticotropin*

as adjuvant in tuberculosis, 76 708-710

-dihydrostreptomycin, in experimental bovine tuberculosis in rabbit, 76 201-211

in emphysema, effect on pulmonary function, 64 279-294

in pneumonia induced with tuberculin in lungs of sensitized rabbits, 64 508-515

-streptomycin-PAS, in pulmonary tuberculosis, 66 542-547

in tuberculosis, 66 161-174

experimental, (Notes) 77 536-538

*Hormones(s), corticotropin cont*

- compared with cortisone, 68 31-41
  - with and without antimicrobial therapy, 70 623-636
  - in humans, request for data, (correspondence) 64 471-472
  - in infancy and childhood, 74 (Supplement, August 209-216)
  - ocular, decreasing dosages in the rabbit, (Notes) 69 1051-1053
  - in tuberculous lesions in guinea pig, 64 295-306
  - in tuberculous meningitis, (case reports) 72 825-832
- cortisone
  - in BCG infection in guinea pig, 69 511-519
  - in cardiopulmonary function in Boeck's sarcoid, 67 154-172
  - in corneal tuberculosis, 74 1-6
  - dihydrostreptomycin, in experimental tuberculosis in guinea pig, (Notes) 67 101-102
  - effect on electrophoretic patterns and hemagglutination reaction in childhood tuberculosis, (Notes) 73 964-965
  - in emphysema, effect on pulmonary function, 64 279-294
  - in experimental tuberculosis, 62 337-344, 65 64-74, 596-602, 603-611
    - in albino rats, compared with alloxan-induced diabetes, 65 603-611
    - compared with corticotropin, 68 31-41
    - growth of tubercle bacilli after, (Notes) 77 529-535
  - in Hamman-Rich syndrome, (case reports) 76 123-131
  - isoniazid in BCG-vaccinated subjects, 76 263-271
  - streptomycin in experimental tuberculosis in albino rats, 65 596-602
  - in tuberculosis, 66 161-171
    - with and without antimicrobial therapy, 70 623-636
    - in humans, request for data, (correspondence) 64 471-472
    - in infancy and childhood, 74 (Supplement, August 209-216)
  - in tuberculous lesions in guinea pigs, 64 295-306
  - in tuberculous meningitis, 64 564-571, (case reports) 73 99-109
- in experimental tuberculosis in mice, 69 790-796
- hydrocortisone
  - acetate ointment
    - topical, at site of intracutaneous tuberculin reaction, (Notes) 79 666-668
    - in tuberculin skin reaction, (Notes) 80 587-589
  - prednisone
    - causing tuberculosis activation, (case reports) 76 140-143
    - in pleural tuberculous effusions, 79 307-314
  - somatotrophic
    - effect on course of tuberculosis in rabbit eye, 69 1016-1021
    - in tuberculosis, (correspondence) 71 319-321
  - testosterone, in chronic pulmonary tuberculosis, 68 165-176, 70 1020-1029
- Horner's syndrome complicating surgery for pulmonary tuberculosis, 67 94-100
- Horse, chronic alveolar emphysema in, 80 (Supplement, July 141-143)
- Hospital(s) *See also* Sanatoriums
  - discharges *See* Discharges
  - Fitzsimons Army Hospital (Denver, Colorado), tuberculin reaction in tuberculous patients, 80 569-574
  - general, case finding in, 70 304-311
  - and home, in tuberculosis, and chemotherapy, 80 (Supplement, October 23-45)
  - military, for tuberculosis, histoplasmosis in, (Notes) 75 833-835
  - personnel, tuberculosis control in, 67 74-84
  - for tuberculosis
    - case finding in, 80 (Supplement, October 73-93)
    - employees, tuberculosis among, 66 16-27
    - isolation of air-borne tubercle bacilli in, (Notes) 67 878-880
    - rehabilitation and occupational therapy in, 79 680
    - vocational rehabilitation in, justification of, 80 59-64
  - tuberculous patients in, adjustment on various wards, 79 273-283
- Household associates, tuberculosis attack and death rates of, 65 111-127
- Humoral factors in resistance to tuberculosis, 76 90-102, 78 884-898
- Hyaluronidase
  - effect on BCG vaccination, 64 142-147, 68 188-198
  - in tuberculosis, 63 108-115
- Hydrazines in production of fatty livers in rabbits, (Notes) 73 956-959
- Hydrocortisone *See* Hormones
- Hydrogen peroxide
  - isoniazid, *M. paratuberculosis* susceptible and resistant to, differential uptake of isoniazid C<sup>14</sup> by, (correspondence) 80 110-111
  - in isoniazid resistance, 73 725-734
- Hydroxyethyl sulfone in pulmonary tuberculosis, 68 103-115
- Hyperergic reactivity, non-specific, at site of tuberculin reaction, 69 205-215

- Hyperplasia, lymph node, of mediastinum, (case reports) 79 232-237
- Hypertension, terminal, with sarcoidosis, (case reports) 60 228-235
- Hyperthyroidism in native resistance to tuberculosis, 79 152-179
- Hypothyroidism in native resistance to tuberculosis, 79 180-203
- Hyperuricemia, during para-aminamide-isoniazid therapy, (Notes) 71 289-292
- Hypnosis, bronchograms under, (Notes) 79 525
- Hypogammaglobulinemia, with steatorrhea and probable tuberculosis, (case reports) 71 773-782
- Hypokalemia and hepatitis in tuberculosis, (case reports) 68 136-143
- Hyponatremia in pulmonary tuberculosis, 66 357-363
- Hypopotassemia in pulmonary tuberculosis, 66 357-363
- Hypoventilation, idiopathic, polycythemia, and cor pulmonale, (case reports) 80 575-581
- Hypoxia, from pulmonary emphysema, hematologic adaptation in, 78 391-398
- I**
- I<sup>131</sup>, radioactive, -labeled 3,5 diiodo PAS, effect on tubercle bacillus, 65 316-324
- Icterus, in miliary tuberculosis, (case reports) 66 77-85
- Ileostomy, nonsurgical, in tuberculous enterocolitis, (case reports) 60 648-653
- Immobilizer, lung, in pulmonary tuberculosis, (correspondence) 67 267, 778-780
- Immunity *See* Tuberculosis, immunity
- Immunology and pulmonary diseases, 79 212-220
- Immunopathology of tuberculosis, 74 (Supplement, August 60-74)
- Index of air velocity *See* Ventilatory function and Pulmonary function
- Index card, for clinical data on patients in a tuberculosis hospital, (Notes) 70 903-906
- Indians (American), tuberculous infection in, 72 35-52
- Industry, roentgenograms in, 60 501-513
- Infant(s)  
pulmonary tuberculosis in, Promizole®-streptomycin in, (case reports) 61 747-750  
tuberculous infection in, (case reports) 70 161-165, (Notes) 74 149-151, (correspondence) 80S-809
- Infarction, pulmonary, location of, 60 206-211
- Influenza *See* Viruses
- Infrared spectrums of fractions of *M. tuberculosis*, 65 477-480
- Inhalation treatment, (editorials) 71 454-456
- Inhibition of tubercle bacilli, tested in synthetic organic bases, (Notes) 65 631-634
- Inoculation, cutaneous, tuberculosis from, 63 526-537
- Inoculum, size in susceptibility testing of *M. tuberculosis*, (Notes) 72 390-392
- Inspissated cavities *See* Cavities
- Insulin, in treatment of anorexia, 60 25-31
- Intermittent positive pressure breathing  
in bronchopulmonary disease, 71 693-703  
in emphysema, pulmonary, severe, 76 33-46  
in pulmonary tuberculosis, 72 479-486
- International Symposium of the Deborah Sanatorium and Hospital, 80 (Supplement, October 1-139)
- International Union Against Tuberculosis, (correspondence), 78 810, report on, 77 155-161
- Intestinal tuberculosis *See* Tuberculosis, intestinal
- Intraperitoneal hemorrhage *See* Hemorrhages
- Iodine  
in leprosy, (correspondence) 68 295-296  
in tuberculosis, (correspondence) 66 765-777
- Iodized oil in bronchography in pulmonary tuberculosis, 66 699-721
- Ions, ammonium, effect on ability of virulent mycobacteria to bind neutral red, (correspondence) 60 384
- Isoniazid  
in *Coccidioides immitis*, (Notes) 67 538  
discontinuance, withdrawal symptoms, 67 212-216  
in murine leprosy, (Notes) 67 674-675  
neurotoxicity in dogs, 69 261-266  
pharmacology, 68 199-206  
resistance of mycobacteria to, (Notes) 65 754-758, 759-760, 76S-770  
in sarcoidosis, ineffectiveness of, (Notes) 67 671-673  
side effects of, (Notes) 68 270-272  
in tuberculosis  
experimental, 65 365-375, 376-391  
human, 65 402-428  
in tuberculous meningitis, 70 714-727
- Iron distribution in tuberculous granulation tissue, 61 560-562
- Irradiation, by sunlamp, effect on *M. tuberculosis*, 71 112-125
- Irregular discharge *See* Discharges
- Isolation, compulsory, of uncooperative patient, (Notes) 77 506-510
- Isoniazid  
absorption, 65 429-442  
Actinomycetales susceptibility to, compared with other synthetic and antimicrobial agents, (Notes) 67 261-264

*Isoniazid, cont*

## action

- antithyroid, (Notes) 71 889-891
- on intracellular tubercle bacilli, 66 125-133
- mode of, 70 784-792, (correspondence) 75 517-518

## activity

- alone, and in combination with streptomycin, 67 808-827
- neutralization of, by metabolites, 73 735-747

allergy, (case reports) 74 783-792

## alone

- and with PAS, in original chemotherapy of noncavitary pulmonary tuberculosis, 80 641-647

in pulmonary tuberculosis, 74 903-916

and combined with streptomycin, 67 808-827

## antagonism

- by antibacterial agents, (Notes) 68 280-283
- by certain metabolites, (Notes) 68 938-939
- delayed by pyridoxine *in vivo*, (Notes) 76 1100-1105

antithyroid action, (Notes) 71 889-891

antituberculosis action, (Notes) 77 364-367

bacterial resistance to, streptomycin effect, 67 553-567

bactericidal action on extracellular and intracellular tubercle bacilli, 67 322-340

bacteriotropic activity with other compounds, (Notes) 78 802-805

bacteriotropic potencies increased by PABA, (correspondence) 78 949-951

in biologic fluids, (Notes) 65 484-485

breakdown, peroxide in, (Notes) 73 779-780

-C<sup>14</sup>

- differential uptake by *M paratuberculosis* susceptible and resistant to isoniazid and hydrogen peroxide, (correspondence) 80 110-111

-labeled PAS, 75 71-82

catalase and peroxidase relation in mycobacteria, 75 62-70

cavities in tuberculosis treated with, 77 221-231

central nervous system reactions to, 69 759-762

as chemoprophylactic in tuberculosis, (correspondence) 74 475-476

clinical evaluation of, (correspondence) 70 1102-1103

in combined chemotherapy of mice, 68 411-418

compared with streptomycin-isoniazid, and streptomycin-PAS in pulmonary tuberculosis, (Notes) 66 632-635, 68 264-269, 67 108-113, 539-543

## concentrations

in blood of people of Japanese and European descent, (Notes) 78 944-948

in culture media, effect of inspissation and storage on, (Notes) 75 678-683

in tuberculous patients, effect of amines on, (Notes) 76 152-158

-cortisone, in BCG-vaccinated subjects, 76 263-271

## -cycloserine

in ambulant tuberculosis therapy, (Notes) 89 94

in pulmonary tuberculosis, (Notes) 79 87-89  
high dosage, treatment-failure, chronic (Notes) 80 269-273

in tuberculosis, 75 553-575

-D-glucuronolactone isonicotinyl hydrazide, inhibitory activity of, 73 892-906

delirium and, (correspondence) 69 845-846

-dependent strains of *M ranae*, (Notes) 68 631-633

derivatives, in experimental tuberculosis, 67 354-365

## determination of

in body fluids, 76 852-861

by urine tests, (Notes) 80 904-908

in development of atypical variants of *M tuberculosis in vitro*, (Notes) 78 921-926

discontinuance, withdrawal symptoms, 67 212-216

distribution, 65 429-442

## dosage, high

in man, 69 957-962

in pulmonary tuberculosis, (Notes) 77 539-542

early treatment in tuberculosis in guinea pigs, 76 732-751

## effect

on allergy, 74 (Supplement, August 197-208)

on bacillary metabolism, 80 404-409

of barbiturates on toxicity of, (Notes) 66 100-103

on BCG allergy, 77 232-244

on *Coccidioides immitis*, (Notes) 67 538

on diabetes, (correspondence) 67 544

emotional, 68 523-534

and electro encephalographic, 70 476-482

on immunizing activity of normal and isoniazid-resistant BCG, (Notes) 75 650-655

inhibitory, on growth of tubercle bacilli antagonized by ketone compounds, (Notes) 68 273-276

on mycobacterial lipids, 72 713-717

on nitrogen metabolism and food intake in nontuberculous patients, 68 207-211

on program of tuberculosis associations, (editorials) 66 615-618

on pyridoxine metabolism, 75 594-600

on tubercle bacilli, growing and resting (Notes) 69 125-127

growth of, from pulmonary lesions, (Notes) 79 518-521

*Isoniazid, effect, cont*

- phase contrast and electronmicroscopic studies of, (Notes) 73 296-300
- proposed mechanism for, (correspondence) 69 1062
- in vitro*, 71 556-565
- on tuberculin reaction and healing of BCG-induced ulcers, 74 7-14
- on tuberculin test, (Notes) 67 535-537
- on viability of *M. tuberculosis*, 69 1022-1028
- excretion, 65 429-442
- and fever, (case reports) 68 249-252
- transitory, and roentgenographic exacerbation from, (case reports) 72 527-536
- hydrazones, in biologic fluids, 79 492-496
- inactivation
  - by Dubos medium, (Notes) 68 284-285
  - by mycobacterial extracts, 72 196-203
- ineffectiveness in microbial persistence, (Notes) 76 1106-1109
- ingestion indicated with riboflavin, (Notes) 80 415-423
- inhibition of, in man, by PAS and benzoyl-PAS, 80 26-37
- and isoniazid-streptomycin, in tuberculosis, incidence of bacterial resistance, (Notes) 67 106-107
- isopropyl derivative *See* Iproniazid
- low concentrations measured by microbiologic assay technique, (Notes) 75 992-994
- metabolism of
  - by *M. tuberculosis* BCG, (Notes) 78 806-809
  - and peripheral neuritis, 70 266-273
  - serum microbiologic assay technique for, (Notes) 75 995-998
  - and sputum conversion, (correspondence) 77 869-871
- in multiple sclerosis, 70 577-592
- in murine leprosy, (Notes) 67 674-675
- neurotoxicity in dogs, 69 261-266
- neutralization by pyridoxal, 76 568-578
- paired with other drug combinations, 80 627-640
- PAS
  - compared with pyrazinamide-isoniazid, 73 704-715
  - effect on thyroid function, 80 845-848
  - salt of, in tuberculosis, (Notes) 78 637-643
  - single daily dose, 78 749-759
  - in tuberculous sinuses and fistulas, 68 535-540
- peripheral neuritis associated with, (case reports) 70 504-505
- peripheral neuropathy in patients treated with, (case reports) 68 458-461
- pharmacology of, 67 644-651, 68 199-206
- in presence of PABA, (correspondence) 76 706-707
- prevention, in experimental tuberculosis, 74 917-939
- in production of fatty livers in rabbits, (Notes) 73 956-959
- prophylaxis
  - effect on tuberculin response, 77 232-244
  - in experimental tuberculosis, (Notes) 77 999-1004
  - in guinea pigs, 73 1-18
  - in nontuberculous disease, (correspondence) 78 485-487
- psychosis, toxic, from, (case reports) 79 799-804
- pyrazinimide,
  - causing hyperuricemia, (Notes) 74 289-292
  - compared with isoniazid-PAS, 73 704-715
  - hepatotoxicity of, in tuberculosis, 80 371-387
  - in low dosage, 74 400-409
  - in patients with previous isoniazid therapy, (Notes) 75 846-848
  - in tuberculosis, (Notes) 72 851-855
  - experimental, 69 319-333
  - pulmonary, 69 319-350, 70 413-422, (Notes) 70 743-747
- pyridoxine
  - concurrently administered, (Notes) 74 471-473
  - effect on antituberculosis activity of, *in vivo*, (Notes) 71 898-899
  - relationship in children, 75 594-600
- radioactive, action on tuberculosis, 67 491-496
- resistance
  - acquired, (Notes) 79 97-101
  - and catalase activity
    - correlated with guinea pig virulence, (Notes) 72 246-251
    - of tubercle bacilli, (Notes) 69 471-472
  - catalase and hydrogen peroxide in, 73 726-734
  - intra strain variation, 73 390-405
  - of mycobacteria to, (Notes) 65 754-774
  - to *M. avium*, (Notes) 77 519-523
  - in pretreatment patients, 72 143-150
  - in relation to pyrogallol-peroxidative activity in *M. tuberculosis*, (Notes) 75 670-674
- resistant
  - cultures, from clinical specimens, virulence of, in guinea pigs, (Notes) 68 290-294
  - mutants, 70 465-475
  - organisms, tuberculous pneumonia due to, (case reports) 70 881-891
  - strains of *M. tuberculosis*
    - peroxide formation in medium for, 75 476-487
    - virulence, 71 799-809
  - tubercle bacilli, 70 91-101, 442-452
  - altered growth characteristics of, (Notes) 66 626-628
  - growth requirements of, (correspondence) 75 155-156
  - catalase and pathogenicity of, 70 641-664
  - hematin as growth factor for, 69 797-805

*Isolated resistance*

- in infection of children 80 326-339
- lesions produced by, regression of, (Notes) 70 531-532
- metabolism of, 71 785-796
- pathogenicity of, in children, 71 (Supplement, August 75-89)
- human, 71 790-105
- pathology of lesions caused by, (Notes) 71 633-637
- in pulmonary tuberculosis, new and untreated, (Notes) 74 293-296
- superinfection with, (case reports) 77 168-171
- virulence of, 68 548-556, (correspondence) 69 640-641, (correspondence) 70 375-376, 70 728-733
- in guinea pigs and mice, (Notes) 69 464-468
- immunizing properties compared with BCG, (Notes) 70 527-530
- Salizid<sup>®</sup>, in the blood, (Notes) 71 796-797
- in sarcoidosis, ineffectiveness of, (Notes) 67 671-673
- serum concentrations
  - and therapeutic response, correlation of, in pulmonary tuberculosis in humans, (correspondence) 80 108-110
  - in tuberculous patients, (Notes) 68 286-289
- serum free, chemical and biologic determination method, 79 311-350
- singly, in murine leprosy, (Notes) 72 846-850
- stability, 71 732-742
- streptomycin
  - action of *M. tuberculosis* within phagocytes, (Notes) 65 775-776
  - antagonism in mice infected with *M. tuberculosis* H37Rv, (Notes) 68 277-279
  - in experimental tuberculous meningitis, 70 714-717
  - in murine leprosy, (Notes) 72 846-850
  - resistance, (correspondence) 75 346-347
  - synergism of, *in vitro*, (Notes) 65 777-778
  - therapy, in fatal meningitis, (case reports) 72 653-658
- in tuberculosis
  - experimental, in guinea pigs, 68 575-582
  - ocular, in rabbits, 69 1016-1021
  - PAS, combinations of
    - therapeutic and toxic effects of, 69 1-12
    - in tuberculosis, 32-week observations on, (Notes) 70 521-526
  - viomycin-streptomycyclidene isonicotinyl hydrazine, in mouse, (Notes) 68 292-294
- streptovaricin
  - controlled clinical trial of, (Notes) 80 757-759
  - in pulmonary tuberculosis, (Notes) 80 424-425, 431-433
- surgical pathology of pulmonary tuberculosis treated by, (Notes) 68 144-149
- susceptible and -resistant *M. tuberculosis* strains, catalase and peroxidase activities of, (Notes) 79 669-671
- susceptibility and pathogenicity of tubercle bacilli, 68 734-738
- therapy
  - in epileptics, hazards of, (case reports) 66 501
  - in tuberculous meningitis, (case reports) 73 940-943, (correspondence) 74 480
- thiocarbanidin, in pulmonary tuberculosis, (Notes) 80 590-593
- toxic psychosis from, (case reports) 79 799-804
- toxicity of, (correspondence) 68 296-297
  - accompanied by leukopenia and lymphocytosis, (case reports) 69 824-828
  - high dosage, 70 430-441
  - and metabolic effects of, in adults, 67 652-656
  - for monkeys, (correspondence) 68 470
  - for rhesus monkey, 67 798-807
  - short term, 65 429-442
- trace metals in inhibition of bovine liver, catalase by, (Notes) 77 501-505
- tuberculin reactions during treatment with, 69 733-744
- in tuberculosis
  - experimental, 65 357-364, 365-375, 376-391, 392-401, 73 1-18, 75 295-302
  - in guinea pigs, 68 75-82
  - infected with tubercle bacilli resistant to streptomycin-PAS, 66 477-485
  - pyridine nucleotides before and during, 70 453-464
  - reinfection in, (Notes) 79 246-250
  - in vivo*, affected by "anti-isoniazid" substance, (Notes) 73 764-767
- fibrocaseous, sputum culture and microscopy during treatment, 70 349-359
- human, 65 402-428, 429-442
- isolation, drug susceptibility, and catalase testing of tubercle bacilli from patients, 70 852-872
- meningeal and miliary, 66 391-415
- primary, prophylactic effects of, 76 942-963
- pulmonary, (correspondence) 70 924-925, (correspondence) 71 314-315, (Notes) 73 117-122
- adrenal cortical function during treatment, 70 841-851
- cystlike cavities during therapy, (Notes) 69 1054-1056
- and electrophoretic serum proteins, 70 334-343
- lesions, pathology of, 71 186-192

*Is used in tuberculous cont*

- long term, 70 228-265
- in monkeys, 71 (Supplement, August 1953)
- prior to resection, 70 102-108
- with pyrazinamide or PAS, (Notes) 70 102-101
- of recent origin, 71 811-859
- tuberculostatic action, antagonized by hemin, (Notes) 69 469-470
- in tuberculous adenitis, (Notes) 71 136-141
- in tuberculous meningitis
  - deleterious effect possible, (correspondence) 71 765-766
  - experimental, 70 714-727
- in tuberculous sinuses and fistulas, 68 535-540
- in vitamin E deficiency, 80 223-231
- Isonicotinic acid, hypothesis of antituberculosis action of isoniazid, (Notes) 77 361-367
- Isonicotinic acid hydrazide *See* Isoniazid
- Isonicotinyl salicylidene hydrazine, and isoniazid in the blood, (Notes) 71 796-797
- Israel, mass roentgenography among immigrants to, (Notes) 69 837-840
- Ivalon sponge plombage, (Notes) 78 478-484

**J**

- Jaundice *See* Icterus
- Jejunum, hemorrhage into, from abdominal aorta through tuberculous lymph nodes, (case reports) 65 210-214
- Jews, tuberculosis among, 67 85-93
- Johnin
  - fractionation of, 68 444-450
  - PPD, cattle erythrocyte sensitization with, (Notes) 77 177-186

**K**

- Kanamycin
  - in murine leprosy, (Notes) 79 673-676
  - in *M. tuberculosis*, (Notes) 78 138-139
  - in humans, 79 72-77
  - in vitro* and in guinea pigs, antituberculosis activity of, 79 66-71
- Kansas City
  - histoplasmin conversion rates as indication of prevalence of infection in, 69 234-240
  - tuberculin conversion rates as indication of prevalence of infection in, 69 227-233
- Ketone compounds, effect on inhibition of growth of tubercle bacilli by isoniazid *in vitro*, (Notes) 68 273-276
- Kidney(s)
  - epithelial cells, sensitivity to PPD and other culture filtrates, 80 410-414

- pyrazinamide spectrophotometric determination in, 75 105-110
- tuberculosis of *See also* Tuberculosis, renal
- roentgenographic classification of, 67 604-612
- viomycin effect on function, 68 511-547
- Kojic acid *See* Acids
- KPAS *See* Potassium para aminosalicylate

**L**

- Laboratory (ies)
  - design and operation for experimental tuberculosis, 68 212-219
  - in tuberculosis sanatorium, (editorials) 73 291-293
- Laryngeal swabs
  - for culture of *M. tuberculosis*, 67 598-603
  - and gastric lavage, in isolation of tubercle bacilli, 73 930-939
- Larynx
  - carcinoma of, with bronchogenic carcinoma, (case reports) 74 438-440
  - nerves of, recurrent paralysis as complication of pulmonary tuberculosis, (case reports) 65 93-99
- Lavage
  - gastric and tracheal, compared in culture of *M. tuberculosis*, 68 926-932
  - tracheal, in diagnosis of pulmonary tuberculosis, 60 634-638
- Leprosy
  - experimental, chemotherapy of, evaluation of drugs, 69 173-191
  - iodine in, (correspondence) 68 295-296
  - murine
    - chemotherapy of, 60 359-365
    - evolution of, (Notes) 79 805-809
    - isoniazid-isoniazid in, (Notes) 67 674-675
    - isoniazid-streptomycin singly and together in, (Notes) 72 846-850
  - kanamycin, streptovaricin, paromomycin, novobiocin, and ristocetin in, (Notes) 79 673-676
  - macrocydon in, (correspondence) 76 915-916
  - Triton WR 1339 in, (correspondence) 76 915-916
- Lesion(s)
  - basic, in chronic emphysema, 68 24-30
  - chest
    - asymptomatic and circumscribed, 62 512-517
    - undetected in mass roentgenographic survey, 64 249-255
  - coalescent, of diatomaceous earth pneumoconiosis, 77 644-667
  - "coin," of lung, (Notes) 73 134-138
  - necrotic, tubercle bacilli in, biology of, (Notes) 66 629-631

*Lesion(s), cont*

## pulmonary

- with atypical acid-fast bacilli in sputum, 75 199-222
- in BCG-vaccinated and unvaccinated persons, 68 695-712
- correlation with tuberculin reaction in BCG-vaccinated and control persons, 68 713-726
- diffuse, roentgenograms of, (correspondence) 60 536-538
- due to *Cryptococcus neoformans*, (case reports) 74 441-444
- importance of tuberculin test in differential diagnosis of, 63 140-149
- isoniazid effect on growth of tubercle bacilli in, (Notes) 79 518-521
- tuberculous
  - amithiozone in, 65 692-708
  - bacteriology of, 74 376-387
  - pathologic study of, 71 (Supplement, March 1-244)
  - resected
    - bacteriology of, 66 36-43
    - clinical and bacteriologic correlation of, 70 689-701
    - culture of *M. tuberculosis* from, comparison of bovine albumin and physiologic saline, (Notes) 70 370-372
    - late emergence of *M. tuberculosis* in cultures of, 70 191-218
    - M. tuberculosis* in, 77 245-259
    - from patients treated with streptomycin-PAS, cultural properties of *M. tuberculosis* in, 68 727-733
    - tubercle bacillus in, 66 44-51
  - spread of, as result of thoracoplasty, 61 648-661
- residual, post-treatment resection of, 73 165-190
- results of thoracoplasty in relation to type of, 60 273-287
- segmental, in primary tuberculosis in childhood, 79 756-763
- tuberculous
  - bacteriologic problems of, 80 (Supplement, October 47-71)
  - bronchial, intra- and extraluminal, 74 (Supplement, August 256-266)
  - bronchoscopy in, (Notes) 73 586-588
  - chronic, in guinea pigs, streptomycin in, 66 194-212
  - effect of streptomycin on morphology of, 61 525-542
  - healing
    - anatomic changes in, (Notes) 72 386-389
    - pathology of, 80 (Supplement, October 47-71)

- pathology and bacteriology of, 74 (Supplement, August 13-21)
- quartz dust for challenging viability of tubercle bacilli in, (Notes) 69 841-842
- produced by isoniazid-resistant tubercle bacilli, regression of, (Notes) 70 531-532
- relapse of, during and after chemotherapy, duration of drug treatment in, 80 (Supplement, October 47-71)
- survival of bacilli in, (Notes) 65 637-640
- vascular, in tuberculous meningitis, 61 247-256
- Leukemia
  - infiltration causing alveolar capillary block, (case reports) 80 895-901
  - with miliary-meningeal tuberculosis, (case reports) 70 509-517
  - pulmonary involvement in, 80 833-844
- Leukocyte(s)
  - from BCG-vaccinated guinea pigs, sonic fragility in, 79 323-328
  - blood, in tuberculin sensitivity, 78 346-352
  - cytolysis
    - "plasma factor" in, (Notes) 79 244-245
    - test, 63 672-673
    - in vitro* by tuberculin, 60 212-222
  - human, sensitivity to OT, 75 807-822
  - lysis, related to tuberculous serology, 69 1002-1015
  - migration, inhibition of, specific and nonspecific, 80 19-25
  - in tissue cultures of normal and tuberculous animals affected by tuberculin fractions, 65 250-271
- Leukopenia, 59 311-316
- Liberia, school-age children of, tuberculin patch-test survey in, (Notes) 67 665-668
- Life-table method, in studies of outcome of chronic disease, (editorials) 63 608-612
- Ligation, suture, and partial thoracoplasty, in pulmonary tuberculosis, 70 61-70
- Light, effect on PAS assay, 75 93-98
- Lipid(s)
  - extraction, biologic properties of mycobacteria after, 79 296-306
  - mycobacterial, isoniazid effect on, 72 713-717
  - of rabbit tissue, in experimental tuberculosis, 75 83-92
  - toxic, of tubercle bacillus ("cord factor")
    - isolation of, from petroleum ether, extracts of young bacterial cultures, 67 629-643
  - occurrence
    - in chloroform extracts of young and older bacterial cultures, 67 828-852
    - in various bacterial extracts, 67 853-858
  - of tubercle bacilli, living and killed, 66 28-35



- Liver**  
 damage  
   in pulmonary tuberculosis, 72 71-90  
   by pyrazinamide, serum enzymes in, 80 855-865  
 derangement, in pulmonary tuberculosis, 76 410-425  
 effect of pneumoperitoneum on, 65 589-595  
 fatty, production in rabbits by hydrazine derivatives, (Notes) 73 956-959  
 peliosis, (case reports) 67 385-390  
 toxicity of pyrazinamide-isoniazid in tuberculosis, 80 371-387  
 in tuberculosis, clinical, functional, and needle biopsy study of, 63 202-209
- Lobar ventilation** *See* Ventilation
- Lobe(s)**  
 anomalous tracheal bronchus to the right upper, (case reports) 64 686-690  
 lower  
   artificial pneumothorax in, 59 50-52  
   disease in pulmonary tuberculosis, 60 15-24  
   pulmonary tuberculosis in, 59 39-49  
   tuberculous cavities in, 63 625-643  
 middle  
   syndrome, 71 775-784  
   traction diverticula of esophagus in, 65 455-464
- Lobectomy**  
 bronchspirometry before and after, 75 710-723  
 in esophagobronchial fistula associated with severe hemorrhages, (case reports) 63 220-226  
 intrapulmonary gas mixing in, 78 1-7
- Löffler's pneumonitis** *See* Pneumonitis
- Löffler's syndrome**, 59 679-686, (case reports) 63 480-486  
 in connection with PAS allergy, 65 235-249, (case reports) 70 171-175
- Los Angeles County (California)**  
 mass screening program in jail, 74 590-596  
 Hospital, routine roentgenography on admission to, 69 940-956
- Lucite plombage** *See* Plombage
- Lung(s)**  
 abscess  
   acute, 61 474-482, 69 673-681  
   in tularemia, (case reports) 65 627-630  
 anatomy  
   microscopic, 80 (Supplement, July 24-40)  
 apex, pulmonary tuberculosis confined to, 63 644-656  
 arterial circulation of, agenesis in, (case reports) 79 641-651  
 beryllium granulomatosis in, 74 533-540  
 biopsy, 71 668-675  
   in pulmonary actinomycosis, (case reports) 76 660-668  
 bullae, function after excision, 77 387-399  
 cancer, 70 763-783  
 carcinoma, primary, of, with tuberculosis, 79 134-141  
 cavitation in periarthritis nodosa, (case reports) 74 624-632  
 circulation *See also* Pulmonary function  
   capillary, 71 822-829  
   and gas exchange, influence of ventilatory mechanics on, 80 53-58  
 "coin" lesions, (Notes) 73 134-138  
 collagen and elastin of, 80 (Supplement, July 45-48)  
 cysts  
   air, giant, surgical management of, (case reports) 63 579-586  
   infected by *M. tuberculosis*, (case reports) 69 1037-1041  
 decortication, in pulmonary tuberculosis, 59 30-38  
 density, as measure of mouse tuberculosis, 77 681-693  
 diffusing capacity *See* Pulmonary function  
 disease  
   alveolar-arterial oxygen tension gradient in, 69 71-77  
   atypical  
     chromogenic mycobacteria in, 75 180-198  
     mycobacterial, 75 199-222  
   from atypical tubercle bacilli, (case reports) 80 738-743  
 blood flow through nonventilated portions, 68 177-187  
 bronchogenic carcinoma as differential diagnostic problem in, 63 176-193  
 chronic  
   from atypical mycobacterial infections, 80 188-199  
   gross, relationship of allergy to, 78 226-234  
   immunologic aspects of, 79 212-220  
   and respiratory function in tuberculosis (Soviet translation), 79 142-151  
 nontuberculous, incorrectly diagnosed, 75 921-937  
 polyvinyl-formal sponge prosthesis in, 74 581-589  
 rheumatoid, (case reports) 80 732-737  
 tracheal fenestration in, 78 815-821  
 distribution of drug-resistant tubercle bacilli in, 73 406-421  
 elastance, application of Hooke's law to, (Notes) 77 863-866  
 emphysema of  
   chronic, energy cost and control of breathing in, 80 (Supplement, July 131)  
   eosinophilia infiltrating, 59 679-686  
   experimental, 80 (Supplement, July 158-167)

*Lungs) emphysema of cont*

variability of behavior within, 80 (Supplement, July 196)  
 and vascular changes, 80 (Supplement, July 67-91)  
 fibrosis  
     carbon monoxide diffusing capacity in, 71 317-312  
     cardiopulmonary function in, 80 700-701  
     diffuse, interstitial, (case reports) 68 603-611, 71 185-510  
 function *See* Pulmonary function  
 hemangiopericytoma of, (case reports) 77 196-500  
 histoplasmosis, diagnosed by scalene node biopsy, (case reports) 66 497-500  
 human  
     preparation for macroscopic and microscopic study, 80 (Supplement, July 114-117)  
     respiratory portion, pre- and postnatal development of, 80 (Supplement, July 5-10)  
 immobilizer, in pulmonary tuberculosis, (correspondence) 66 778-780  
 infiltration *See also* leukemia, below  
     disseminated, nodular, indeterminate in apparently healthy persons, 65 128-141  
     with histoplasmin sensitivity, 59 636-642  
 inflammation  
     chronic, interstitial, with fibrosis, and bronchiolar carcinoma, 76 559-567  
     nontuberculous, effect on pulmonary tuberculosis, 59 68-75  
 inflation or deflation in respiration regulation, 73 519-528  
 insufficiency  
     chronic, radioactive iodine ( $I^{131}$ ) in, 80 181-187  
     prevention of, after pleurisy, 66 134-150  
 in leukemia  
     infiltration of, causing alveolar capillary block, (case reports) 80 895-901  
     involvement, 80 833-844  
 lymphatics of, in reference to emphysema, 80 (Supplement, July 50-56)  
 malignancy *See also* Tumors  
     cytologic diagnosis of, 61 60-65  
     and eosinophilia, (case reports) 75 644-647  
     mucormycosis of, (case reports) 79 357-361  
     mycotic diseases of, in India, (Notes) 78 644-646  
     nodules, calcified, in relation to bronchogenic carcinoma, 66 151-160  
     normal, blood flow through nonventilated portions, 68 177-187  
     physical properties of, 80 38-45  
     pneumoperitoneum in, physiologic effects of, 60 706-714  
     pneumothorax in, 64 1-20, 21-26, 27-40, 127-140, 141-150, 151-158

post-thoracoplasty, resected, 60 406-418  
 proteinosis, alveolar, of, (case reports) 80 249-251  
 resection  
     bronchial ulceration after, 69 84-91  
     pulmonary function before and after, 72 453-461  
     for pulmonary tuberculosis, bronchial disease in, 68 657-677  
 sarcoidosis of, evolution of, (case reports) 80 71-77  
 schistosomiasis of, chronic, 79 119-133  
 -specific antibodies, in rabbits, 78 259-267  
 specimens  
     methyl-metacrylate in, 76 789-798  
     occult tuberculous endobronchitis in, 77 931-939  
 structure, in three dimensions after inflation and fume fixation, 79 764-772  
 susceptibility to industrial dusts inhaled, 62 (Supplement, July 13-21)  
 suture in tuberculosis, 70 61-70  
 tissue, viability of tubercle bacillus in, 59 429-437  
 trauma at pneumothorax induction, 60 557-563  
 tuberculoma of, 78 403-410  
 tuberculous *See also* under Tuberculosis  
     focus, primary, of, local reactivation in, 78 547-562  
     gas mixing in, 74 343-350  
     resection  
         in Hawaii, 80 6-11  
         histologic study of blood vessels in, 64 489-498  
 tumor *See* Tumors  
 vascular changes, in pulmonary tuberculosis, 75 410-419  
 ventilation, defective, analysis by timed capacity measurements of, 64 256-278  
 Lupus erythematosus  
     cells  
         in miliary tuberculosis, (case reports) 74 112-116  
         in sarcoidosis, (correspondence) 74 811  
     surgery in, (case reports) 77 338-345  
 Lupus vulgaris cutis, fatality ratio for, 80 659-675  
 Lymphadenitis  
     mesenteric, complication of, (case reports) 65 210-214  
 tuberculous  
     cervical, X-ray therapy in, (Notes) 74 641-644  
     peripheral, X-ray therapy for, 68 157-164  
     sodium salicylate in, (correspondence) 68 940-941  
     treated by tuberculin desensitization, (case reports) 60 249-257

- Lymphadenopathy**  
 intrathoracic, transient, in apparently healthy persons, 67 45-55  
 scalene, (Notes) 76 503-505
- Lymphatics**  
 as drainage for parietal and visceral pleura, 79 52-65  
 pulmonary, in reference to emphysema, 80 (Supplement, July 50-56)  
 role in development of bronchogenic tuberculosis, 67 440-452
- Lymph node(s)**  
 causing hemoptysis, removal of, (case reports) 65 206-209  
 giant, hyperplasia of mediastinum, (case reports) 79 232-237  
 hilus, calcified, 60 1-14  
 mediastinal, calcified, 62 213-218  
 regional, calcification of, after BCG vaccination, 73 239-245  
 sarcoid, effect on tubercle bacilli of products of, 61 730-734  
 tuberculous, in children, enzymatic therapy for, 76 588-600  
   complications, 70 610-622  
   hemorrhage from abdominal aorta into jejunum through, (case reports) 65 210-214  
   in neck, axilla, and groin, 73 229-238  
   treatment in accessible nodes, (editorials) 64 691-694
- Lymphosarcoma** *See* Tumors
- Lysis, cellular, in tuberculin sensitivity, 68 746-759**
- Lysozyme(s)**  
 action on mycobacteria, 68 564-574  
 lethal and cytologic effects on tubercle bacilli, 67 217-231  
 tuberculostatic substance in serum with properties like, 64 669-674
- Lytic factor, against *M. tuberculosis*, (Notes) 72 859-862**
- M**
- Macacus irus*** *See* Monkeys
- Macrocydon, in murine leprosy, (correspondence) 76 915-916**
- Madison sentence-completion form, (Notes) 74 964-967**
- Malachite green**  
 effect on growth of *M. tuberculosis*, 74 50-58  
 and Triton WR 1339, in charcoal media for tubercle bacilli, (Notes) 71 894-897
- Malignancy(ies)** *See also* Cancer, Tumors  
 pulmonary, cytologic diagnosis of, 61 60-65
- Marine Corps, tuberculin testing in, 62 518-524**
- Marsihd®** *See* Ipromazid
- Maryland, University of, tuberculosis in medical students at, 79 746-755**
- Masks, gauze, efficiency of, 59 1-9**
- Maximal breathing capacity** *See also* Pulmonary function  
 in obese subjects, (Notes) 80 902-903  
 spirometric and Douglas Bag measurement comparisons, (Notes) 79 253-255
- Maximal expiratory flow rate apparatus for bedside and office use, 80 724-731**
- Maximal minute expiratory flow, 72 783-800**
- Measles, and BCG vaccination, (case reports) 72 228-230**
- Media** *See* Medium(a)
- Mediastinum**  
 cysts of, and neoplasms in children, 74 940-953  
 electrocardiogram after, shift to the left in, 64 64-70  
 emphysema of  
   complicating induction of pneumoperitoneum, (case reports) 63 591-596  
   after pneumoperitoneum, (case reports) 68 775-781  
 lymph nodes in  
   calcified, (case reports) 62 213-218  
   hyperplasia of, (case reports) 79 232  
 tuberculoma of, 64 327-352  
 tumors of, 60 419-438  
   cardiospasm simulating, (case reports) 63 597-602
- Medical schools, teaching of tuberculosis in, (editorials) 60 140-142**
- Medical students, tuberculosis in, at University of Maryland, 79 746-755**
- Medium(a)**  
 agar, transparent, growth and enumeration of mycobacteria in, 64 81-86  
 artificial, used for detection of small numbers of tubercle bacilli from dispersed cultures, 65 572-588  
 chick embryo compared with ATS medium in isolation of tubercle bacilli, (Notes) 76 703-705  
 contrast, water soluble, in bronchography, 68 760-770  
 culture  
   artificial, isolation of *M. tuberculosis* on, (Notes) 70 912-915  
   charcoal  
     for *M. tuberculosis*, 71 382-389  
     drug susceptibilities, (Notes) 71 447-451  
     for tubercle bacilli, 70 955-976  
     Triton WR 1339 and malachite green in, (Notes) 71 894-897  
   for *M. tuberculosis*, blood bank blood agar, (Notes) 71 762-764  
   for tubercle bacilli, for diagnosis, 63 459-469  
   comparison of several media, 63 470-475

*Medium(s), cont***Dubos**

- inactivating isoniazid, (Notes) 68 284-285
- with penicillin
- instability of, (Notes) 80 262-263
- for isolation of *M. tuberculosis* from human discharges, (Notes) 61 318-321

**egg**

- case laid, elimination of preclearing, (Notes) 79 677

- cultivation of tubercle bacilli, (Notes) 73 139-141

**egg-yolk, for tubercle bacilli, 70 977-988**

- glycerol blood agar, response of acid fast chromogenic bacilli, 72 119-122

**liquid, growth of *M. tuberculosis* in, 73 716-725**

- liquid and solid, for detection of streptomycin resistance in *M. tuberculosis*, 62 101-108

- relationship to growth, morphology, and virulence of *M. tuberculosis* var *anatum*, 66 567-577

- semisynthetic, autoclavable, in tuberculosis laboratory, (Notes) 78 788-792

- solid, for testing streptomycin susceptibility, 62 484-490

- synthetic, liquid, new, for cultivation of *Mycobacterium* species, (Notes) 80 267-268

- Triton malachite green-charcoal agar, (Notes) 75 338-339

**Mega-esophagus See Achalasia****Meningeal tuberculosis See Tuberculosis, meningeal****Meningitis**

- bacterial, streptokinase-streptodornase in, 71 12-29

- cryptococcal and tuberculous, in reticulum cell sarcoma, (case reports) 78 760-768

- with miliary tuberculosis and leukemia, (case reports) 70 509-517

- pneumococcal, combined with tuberculous, (case reports) 71 584

- pyogenic, with tuberculous meningitis, (case reports) 62 441-445

- serous intracranial, calcification after, (case reports) 78 101-105

**tuberculous, (correspondence) 78 485**

- in adults, 74 830-834

- streptomycin-treated, 67 613-628

- antimicrobial drugs in, 69 192-204

- in children, 76 832-851

- combined with pneumococcal, (case reports) 71 584-591

- corticotropin in, (case reports) 72 825-832

- cortisone in, (case reports) 73 99-109

- after cortisone therapy, 64 564-571

- discussion, (Notes) 65 637-640

- effect of induced hyperglycemia on glucose content of cerebrospinal fluid in, 67 59-73

- experimental, isoniazid, iproniazid, streptomycin, and isoniazid-streptomycin in, 70 714-727

- fatal, during isoniazid-streptomycin therapy, (case reports) 72 653-658

- in guinea pigs, produced by lumbar intrathecal inoculation, 66 722-731

- intracranial calcification after, 78 38-61

- isoniazid in, deleterious effect possible, (correspondence) 71 765-766

- during isoniazid therapy, (case reports) 73 940-943, (correspondence) 74 480

- neomycin failure as adjuvant to streptomycin, (case reports) 65 325-331

- neoplastic disease simulating, (case reports) 69 1029-1036

- pathogenesis of, 64 408-418

- pathology of, 61 171-184, 64 419-429

- pneumoencephalography in, 74 835-855

- during pregnancy, (case reports) 76 1079-1087

- prognosis of, 65 168-180

- and treatment, 80 388-397

- with pyogenic meningitis, (case reports) 62 441-445

- reaction to PAS simulating, (case reports) 64 682-685

- with spontaneous recovery, (case reports) 72 231-235

- streptodornase streptokinase in, 71 12-29

- streptomycin therapy in, 61 171-184, 62 586-593

- therapy, specific, for, (editorials) 61 263-268

- treatment of, 69 370-382, 74 (Supplement, August 221-224)

- results in 549 patients, 69 13-25

- tuberculin in, (case reports) 74 277-283

- vascular lesions in, (case reports) 61 247-256

- in vitro* susceptibility of tubercle bacilli in, 74 (Supplement, August 232-240)

**Mental patients**

- tuberculosis morbidity and mortality among, 70 32-48

- tuberculous, reserpine in, (Notes) 74 457-461

**Mesenchyma, extrapleural, (case reports) 75 638-643****Mesothelioma See Tumors****Metabolism**

- bacillary, effect of isoniazid on, 80 404-409
- carbohydrate, associated with amithiozone, (case reports) 66 373-377

- nitrogen, in nontuberculous patients receiving isoniazid, 68 207-211

- of tubercle bacillus, production of a pharmacologically active metabolite, 63 100-107

- Metabolite(s)  
 of *M. tuberculosis* H37Rv and H37Ra, differential response to, (correspondence) 62 333  
 neutralization by, of isoniazid activity, 73 735-747
- Methanol extracts  
 of tubercle bacilli, (correspondence) 74 807-808  
 immunizing effect on mice, (Notes) 73 781-784
- Methemoglobin, and hemoglobin values in tuberculous patients on isoniazid therapy, (Notes) 68 286-289
- Methemoglobinemia following treatment with PAS, (case reports) 76 862-866
- Methylene blue reduction time of serum, tuberculosis influence on, (Notes) 70 907-909
- Methyl-metacrylate, in lung specimens, 76 789-798
- Mice  
 antituberculosis chemotherapeutic activity in, 64 541  
 antituberculosis immunity and nutrition in, 77 93-105  
 brains, *Mycobacterium X* in, 71 88-96  
 lesions of, 71 97-111  
 immunity, sex differences in, 75 618-623  
 infection with tubercle bacilli, relation between dosage and survival time, 64 534-540  
 intravenously infected, isolation of tubercle bacilli from feces and gastric contents, 62 481-483  
 nonpathogenic, viable tubercle bacilli in, 75 280-294  
 PAS-streptomycin therapy in, 62 156-159  
 thioureas, substituted, in tuberculosis in, 70 121-129  
 Triton A-20 in antituberculosis activity in, 65 718-721  
 tubercle bacilli in  
 small numbers detected in dispersed cultures, 65 572-588  
 virulent, detected when coexisting with attenuated bacilli, 70 1053-1063  
 in tuberculosis, experimental  
 antagonism of isoniazid-streptomycin in, (Notes) 68 277-279  
 controlled with intermittent streptomycin, viomycin, isoniazid, and streptomycin hydrazide isonicotinyl hydrazine, (Notes) 68 292-294  
 isoniazid in, 65 357-364, 376-391, 392-401  
 combined chemotherapy with, 68 411-418  
 pyrazinamide in, 65 511-518
- tuberculous  
 BCG in, 68 451-454  
 tuberculin shock in, (Notes), 68 629-630  
 vaccination with BCG, *n*-hexadecane as adjuvant, 75 624-629
- Microbial persistence modified by isoniazid, (Notes) 76 1106-1109
- Micrococcus pyogenes* var *aureus*, sensitization of guinea pigs to, in presence of "wax" of acid fast bacilli, 69 241-246
- Microculture, in blood of tubercle bacilli in pathologic specimens, (correspondence) 73 785-786
- Microculture method for isolation of tubercle bacilli, (Notes) 75 1007-1008
- Microolithiasis, pulmonary alveolar, (case reports) 75 122-131
- Microorganism(s)  
 acid-fast  
 growth characteristics of, (Notes) 80 744-746  
 procedure for differentiating between, 76 468-479  
 viomycin activity against, *in vitro* and *in vivo*, 63 17-24
- Microradiography, in emphysema, 80 (Supplement, July 104-112)
- Microscopy  
 and culture of *M. tuberculosis*, in BCG-vaccinated mice, 79 484-491  
 electron  
 effect of PAS-isoniazid-viomycin on tubercle bacilli, (Notes) 73 296-300  
 in study of mycobacteriophages, 76 964-969  
 of tubercle bacilli, streptomycin-treated, 70 328-333  
 fluorescence, of *M. tuberculosis*, 65 709-717  
 of *M. tuberculosis*, from sputum of isoniazid-treated patients, 70 349-359  
 phase contrast, of corneal tuberculosis, 74 1-6
- Middle age, resection in, 73 40-51
- Middlebrook-Dubos hemagglutination test *See* Hemagglutination
- Middlebrook-Dubos titer, and serum protein electrophoretic pattern in BCG-vaccinated tuberculous children, (Notes) 79 522-524
- Middle lobe syndrome, roentgen therapy in, (case reports) 76 291-297
- Miliary tuberculosis *See* Tuberculosis, miliary
- Military personnel of World War II, pulmonary tuberculosis in, 75 1-40
- Military tuberculosis hospital, histoplasmosis in, (Notes) 75 833-835
- Miners, coal *See* Pneumoconioses, anthracite
- "Minimal," soplustry in use of the word, (correspondence) 79 681
- Minimal tuberculosis *See* Tuberculosis, minimal
- Mitochondria, and nuclei in *M. tuberculosis*, 67 59-73
- Monaldi procedure, 65 83-87
- Moniliasis *See* Mycoses

## Monkey(s)

- effect of alteration of pulmonary arterial circulation on tuberculosis in, 65 48-63
- isoniazid toxicity for, (correspondence) 65 470
- Mycobacterium multum* antituberculosis therapy in, 76 225-231

*Mycobacterium H. capri* lat. in, (Notes) 75 849-851

## rhesus

- isoniazid toxicity for, 67 794-807
  - pathogenicity of atypical chromogenic bacteria for, 75 169-179
  - tuberculosis in, 72 204-209
- Monocytes, immunity studies with, 70 221-231
- Mononucleosis, infectious, simulated by PAS reaction, (case reports) 72 833-839

## Morbidity

- rates, in tuberculosis, 61 39-50
- in household associates, 65 111-127
- tuberculosis
  - among mental patients and general population, 70 32-48
  - related to tuberculin sensitivity and body build, 76 517-539
- trend, 67 270-285

Morphology of fat in tuberculosis in childhood, 71 (Supplement, August 7-12)

## Mortality

- rates, in tuberculosis, 61 39-50
- in household associates, 65 111-127
- tuberculosis
  - among mental patients and in general population, 70 32-48
  - among residents of large cities (1947-1949), 66 109-116

## Mouse See Mice

Mouth wash, detection of tubercle bacilli in, 71 371-381

Mucin, hog gastric, in experimental tuberculosis, (Notes) 77 1005-1011

Mucoid impaction of the bronchi, 76 970-982

Mucoproteins in pleural effusions, 76 247-255

Mucormycosis See Mycoses

Mucosa, bronchial, regenerative versus atypical changes in, 79 591

Multiple sclerosis, isoniazid in, 70 577-592

Murmur, millwheel, presumably caused by air embolism in pneumoperitoneum, (case reports) 70 1092-1095

Myasthenia gravis, with malignant thymoma, (case reports) 72 381-385

## Mycobacteria

- affected by Su 1906, Su 3068, and Su 3912, 77 694-702
- amithiozone resistance and action in, mechanism of, 80 559-568
- arithmetic linear growth of, 66 756-761
- asparaginase of, (Notes) 70 920-921

## atypical

- antimicrobial effect on, 78 454-461
- characterization by microcolonial test, 76 151-167
- comparative pathogenicity of, in experimental animals, 80 876-885
- in HeLa cells, 77 968-975
- infections from chronic pulmonary disease from, 80 188-199
- isolation of
  - from healthy persons, (Notes) 80 747-749
  - and *Nocardia*, 76 451-467, 468-479
- niacin production of, 77 669-674, 675-680
- atypical chromogenic
  - fluid thioglycollate medium in, (Notes) 77 356-358
  - pathogenicity of, for rhesus monkey, 75 169-179
  - in pulmonary disease, 75 180-198
- avirulent, metabolism of, 66 416-435
- biologic properties after lipid extraction, 79 296-306
- carbolfuchsin stained, in diagnostic films, 74 597-607
- catalase enzyme of, 77 146-154
- in cell and tissue cultures, 77 789-801
- cells, crude, biologic activity of, (Notes) 80 274-276
- in chick embryo, influenced by temperature, 73 650-673
- from cold blooded animals, 77 823-838
- communion by ultrasonic exposure, (correspondence) 76 914-915
- comparison between atypical and selected strains, (Notes) 76 497-502
- cooperative study, (correspondence) 72 866-870
- cord formation and virulence, 78 83-92
- coding and cytochemical reaction, 73 674-680
- enzymatic characteristics of suspensions of, (correspondence) 61 270-271
- extracts in inactivation of isoniazid, 72 196-203
- filtration, from organic solvents, 77 290-300
- fluorescence microscopy in detection of, in tissue sections, 68 82-95
- in fowl embryos, 73 276-290
- genetics of, detection of small numbers of virulent tubercle bacilli when co-existing with attenuated bacilli in the mouse, 70 1053-1063
- growth of
  - and enumeration, in transparent agar medium, 64 81-86
  - oxygenation and aeration effect on, 70 665-671
  - rates, in biochemical studies, (Notes) 79 94-96
- infection, mycobacterial, heterologous and homologous immunity in, 76 76-89
- lysozyme action on, 68 564-574

*Mycobacteria cont*

- and mammalian cells in tissue culture, (correspondence) 75 317-318
- metabolism, relationship of isoniazid to, 75 62-70
- in mice, influenced by temperature, 73 650-673
- neomycin activity on, 60 78-89
- neutral red reactions on, (Notes) 79 526-530
- niacin test in distinguishing, (Notes) 79 663-665
- nonpathogenic, as source of error in diagnosis and drug susceptibility tests, 68 557-563
- oxidation reduction dyes in determining virulence, *in vitro*, 65 187-193
- paratubercle bacilli, skin reaction to products of, 79 731-737
- photochromogenic, infections with, chemotherapy and pathology, 80 522-534
- precipitins of, agar diffusion, 73 637-649
- preservation of, by desiccation *in vacuo*, 60 621-627
- purine enzymes in, (Notes) 66 240-243
- resistance to hydrazines of isonicotinic acid, (Notes) 65 754-774
- saprophytic
  - fluid thioglycollate medium, (Notes) 77 356-358
  - and tubercle bacilli, differentiation of, (Notes) 74 948-960
- species, new synthetic liquid medium for cultivation of, (Notes) 80 267-268
- in tissues, retention and differentiation of, 74 608-615
- typical, niacin production of, 77 669-674, 675-680
- virulence of
  - effect of ammonium ions on ability of, to bind neutral red, (correspondence) 60 384
  - metabolism, 66 416-435
  - oxidation-reduction dyes for determination of, (correspondence) 66 382-383, 68 786-787
- in vitro*
  - modification of oxidation reduction dye test for determination of virulence of, (Notes) 66 99, 69 599-603
- Mycobacteriaceae, urease activity in, (Notes) 65 779-782
- Mycobacteriophage(s)
  - biologic properties of, 80 543-553
  - D-29, inhibition of, with human tubercle bacilli, by serum factor, 80 12-18
  - electron microscopic studies of, 76 964-969
- Mycobacterium*
  - avium*
    - drug resistance relationship to growth phase, (Notes) 76 298-300
    - isoniazid resistant, (Notes) 77 519-523
    - relationship of medium to growth, morphology, and virulence, 66 567-577
  - sulfathiazole resistant, in prevention of streptomycin resistance, (Notes) 76 301-307
  - balnei*, in mice, immunity, heterologous and homologous, 76 76-89
  - butyricum*, temperate bacteriophage from, 80 232-239
  - fortuitum*, 72 53-63
    - bacteriology and pathogenicity for laboratory animals, 76 108-122
  - leprae*, separation from tissues by enzyme digestion, (Notes) 74 152
  - leprae murium*, microbial population counts with anti leprosy drugs, 69 173-191
  - paratuberculosis*
    - chemical constituents of, (Notes) 77 712-715
    - susceptible and resistant to isoniazid and hydrogen peroxide, differential uptake of isoniazid-C<sup>14</sup> by, (correspondence) 80 110-111
  - phlei*, specificities of aqueous and saline extracts, 73 563-570, 571-575
  - ranac*, cross resistance to 28 antimycobacterial agents, 69 267-279
  - isoniazid dependent strains, (Notes) 68 631-633
  - neomycin and dihydrostreptomycin resistance in, 62 286-299
- smegmatis*
  - metabolizing glucose, (Notes) 73 589-592
  - stained with indicator dyes, phagocytosis of, 74 552-565
  - streptomycin inhibiting growth of, 71 743-751
- tuberculosis* See also Tubercle bacilli
  - action of cycloserine on, *in vitro*, (Notes) 72 236-241
  - antituberculosis drugs in, combined, (Notes) 78 121-126
  - autolysis, glucose and oxygen in, 73 907-916
  - BCG, metabolism of isoniazid by, (Notes) 78 806-809
  - $\beta$ -propylal- $\gamma$ -butylal-imine inhibiting, (Notes) 76 1094-1096
  - bovine, in experimental tuberculosis, 68 220-228
  - catalase activity, 78 735-748
  - chick yolk sac technique in, (Notes) 77 511-515
  - constituents, 61 798-808
  - correlation of biologic properties with infrared spectrums, 65 477-480
  - cultural properties, in resected pulmonary lesions of patients treated with streptomycin-PAS, 68 727-733

*Mycobacterium, tuberculosis, cont*

- culture
  - chamber method, (Notes) 72 393-397
  - charcoal, 71 382-389
  - colorimetric catalase test in, (Notes) 71 305-307
  - compared with mouse and guinea pig inoculation, 69 92-103
  - comparison of laryngeal swabs and gastric aspiration for, 67 598-603
  - comparison of tracheal and gastric lavage in, 68 926-932
  - medium for, blood-bank blood agar, (Notes) 71 762-764 *See also* Medium(a)
  - method, (Notes) 69 304-306
  - negative, procedure with, (correspondence) 69 128
  - obtained by incubation beyond the normal 7- or 8-week period, (Notes) 69 307-308
  - preservation by freezing, 62 99-100
  - purified tuberculin fraction from, (Notes) 69 300-303
  - from resected lesions, comparison of bovine albumin and physiologic saline in, (Notes) 70 370-372
  - by slide-culture method, 72 330-339
  - sputum for, obtained during local anesthesia, (Notes) 74 977
  - urine, during chemotherapy, 70 149-154
- dissociation, 62 (Supplement, July 22-33)
- drug susceptibilities, (Notes) 71 447-451
  - rapid method for determination, (Notes) 78 111-116
- results of *in vitro* test for, 63 679-693
- enzymatic reactions of, and action of streptomycin, 65 722-734
- filterable forms, (correspondence) 69 473-474
- fluid thioglycollate medium in, (Notes) 77 356-358
- fluorescence microscopy in, 65 709-717
- generation time on solid and liquid media, 74 50-58
- growth
  - delayed, from resected lung specimens, (correspondence) 71 319
  - in liquid media, 73 716-725
  - measurement, 62 87-90
  - from resected specimens under various atmospheric conditions, (Notes) 70 910-911
- H37Ra strain, mechanical agitation in growth of, (Notes) 79 813-815
- H37Rv strain
  - activity of antituberculosis drugs, 59 461-465
  - catalase activity, (Notes) 80 257-258
  - development of atypical variants *in vitro* with isoniazid-streptomycin, (Notes) 78 921-926
  - leukocytic susceptibility to tuberculin in guinea pigs infected with, (Notes) 76 888-891
  - mutant, protein precipitated by, (correspondence) 77 1031-1032
  - specificities of aqueous and saline extracts, 73 563-570
  - in HeLa cells, 77 423-435
  - infection in mice, 73 251-265
  - infrared spectrums of, 63 372-380, 69 505-510
  - isolation of
    - on artificial media and embryonated eggs, (Notes) 70 912-914
    - in egg yolk media, (Notes) 72 863-865
    - from human discharges, use of Dubos-type medium containing penicillin, (Notes) 64 318-321
  - microculture technique, (Notes) 73 576-580
- and isoniazid
  - action within phagocytes, (Notes) 65 775-776
  - activity in, neutralized by metabolites, 73 735-747
  - inhibition by pyridoxal, 76 568-578
  - resistance, 70 442-452
    - hemin as growth factor for, 69 797-805
    - peroxide formation in media for, 75 476-487
  - strains, virulence of, 71 799-809
- susceptible and -resistant strains, catalase and peroxidase activities, (Notes) 79 669-671
- kanamycin in, (Notes) 78 138-139
- lack of significant *in vitro* susceptibility to pyrazinamide on solid media, (Notes) 67 391-395
- late emergence in cultures of resected lesions, 70 191-218
- lipids, infrared spectroscopic examination of, 73 529-538
- lung cyst infected by, (case reports) 69 1037-1041
- lytic factor against, (Notes) 72 859-862
- medium(a) *See* Medium(a)
- metabolism, isoniazid effect on, 80 404-409
- metabolites, differential response to, (correspondence) 62 333
- neomycin activity, 60 78-89
- nuclei and mitochondria in, 67 59-73
- PAS-resistant, (Notes) 77 346-349
- persistence, in drug-treated animals, 77 473-481
- photosensitivity, 71 112-125
- "plasma factor" in leukocyte cytolysis in



*Mycobacterium, tuberculosis, cont*

- guinea pigs sensitized with, (Notes) 79 244-245
- preservation of cultures by freezing, (Notes) 61 696-697
- protein fraction, 66 314-331
- in relation to *B. abortus*, (correspondence) 74 478
- in resected lesions, 77 245-250
- resistance
  - to drugs, 61 483-507
  - of monocytes to, 77 436-449
  - to streptomycin
    - in children, 66 63-76
    - medium for detection, 62 101-108
- resistant strain, effect of Triton A-20 and pH on streptomycin susceptibility of, 62 91-98
- self-inoculation by a diabetic woman with, (case reports) 69 818-823
- sexual cycle, possibility of, (correspondence) 63 721
- slide culture method for detection, 60 51-61
- in sputum, detected by pepsin digestion and interface concentration with pentane, (Notes) 75 148-152
- stained with indicator dyes, phagocytosis, 74 552-565
- streptomycin
  - dependent strains, (correspondence) 59 219-220
  - resistant, 59 438-448
  - susceptibility to, 61 705-718
    - effect of Triton A-20 and pH on, 62 91-98
    - plate method for determining, 61 578-581
    - in vitro*, 59 336-352
- sunlamp irradiation effect on, 71 112-125
- utilization of asparagine as source of nitrogen for growth, 68 127-135
- vaccines from gamma-irradiated, and from *Brucella suis*, (Notes) 79 374-377
- Vallée, isoniazid-resistant mutant, immunizing properties of, as compared with BCG, (Notes) 70 527-530
- viability of
  - in embalmed human lung tissue, 59 429-437
  - in isoniazid, 69 1022-1028
  - in isoniazid-treated lesions, 70 102-108
- viomycin
  - active against, 63 1-4
  - effect on, *in vitro* and *in vivo*, 63 17-24, 25-29
- virulence
  - in chick embryo, 74 249-257
  - by intracasternal test, 76 426-434
  - microcolonial test for, 71 361-370
- vitamin analogues affecting, 62 (Supplement, July 34-47)

*in vivo* and *in vitro* observations on, 74 428-437

*in vitro*, trypsin effect on, 76 279-285

Zephiran® in isolation of, (Notes) 74 284-288

*tuberculosis 607*

effect of nitrogen on growth, riboflavin production and synthesis of a pharmacologically active metabolite, 68 119-126

metabolism, 71 260-265

*ulcerans*

infections, chemotherapy in, 75 266-279

in mice, heterologous and homologous immunity in, 76 76-89

*X*

infectivity and immunogenicity of, in mice, 79 47-51

in mouse brains, lesions of, 71 88-96

*Mycoses* See also Fungi and Fungal antigens

*actinomycosis*

chemotherapy in, 63 441-448

pulmonary, diagnosed by lung biopsy, (case reports) 76 660-668

aerosol amphotericin B in, (Notes) 80 441-442

blastomycosis, systemic, and chemotherapy in pulmonary tuberculosis, (case reports) 68 615-621

coccidioidal cavity, recurrence after resectional surgery, (case reports) 71 131-136

coccidioidal granuloma, acute, disseminated, (case reports) 63 476-479

coccidioidomycosis, 73 501-518

acute disseminated coccidioidal granuloma, (case reports) 63 476-479

contagiousness, 61 95-115, (correspondence) 441

in contacts, 59 632-642

infection in guinea pigs by contact with diseased animals, 61 106-115

spherules in sputum exposed out of doors, 61 95-105

disseminated, 75 828-832

and tuberculosis, 59 415-428

experimental, nystatin in, 72 64-70

pulmonary, (correspondence) 61 158

coccidioidin skin reaction, (case reports) 79 78

coexistent with tuberculosis, 67 477-489

with lymphosarcoma and alveolar-capillary block, (case reports) 78 468-473

surgery in, complications, 77 17-21

and tuberculosis

concomitant, (case reports) 61 887-891

pulmonary, 70 109-120

cryptococcal and tuberculous meningitis complicating reticulum cell carcinoma, (case reports) 78 760-768

Worse, cont

- cryptococcosis, pulmonary, (case reports) 69 116-120
- fungal disease existing with pulmonary tuberculosis, (case reports) 72 667-671
- geotrichosis, pulmonary, (case reports) 76 286-290
- histoplasmosis, (case reports) 67 376-384, 77 719-763
  - acute, benign, (case reports) 69 625-630
  - with Addison's disease and pulmonary tuberculosis, (case reports) 72 675-684
  - causing broncholithiasis, (case reports) 77 162-167
- cavitary
  - chronic, progressive, clinical aids in diagnosis, 75 938-948
  - progressive, in tuberculosis hospitals, 73 609-619
- chronic, 72 274-296
- communicability of, 63 538-546
- diagnostic aids in, (case reports) 70 360-362
- epidemics, 68 307-320
- lung nodules in, surgical significance of, (case reports) 69 829-836
- in military tuberculosis hospital, (Notes) 75 833-835
- prevalence, histoplasmin conversion rate as indication of, 69 234-240
- pulmonary, 67 153-176
  - chronic
    - chemotherapy in, 75 912-920
    - in pregnancy, with spontaneous pneumothorax, (case reports) 75 111-121
    - diagnosed by scalene node biopsy, (case reports) 66 497-500
  - pulmonary cavitation due to, (case reports) 69 111-115
  - roentgenographic patterns in, 76 173-194
  - small outbreak, 78 576-582
  - vena caval obstruction by, (case reports) 77 848-857
- moniliasis, pulmonary, (case reports) 77 329-337
- mucormycosis, pulmonary, (case reports) 79 357-361
- laboratory diagnosis of, 61 690-704
- nocardiosis
  - chemotherapy for, 63 441-448
  - pulmonary, 73 485-500
- Mycostatin® See Nystatin
- Myocardium, tuberculosis of, (case reports) 74 99-105
- heart block change in, (case reports) 65 332-338
- Myvisone See Amithiozone, Thiosemicarbazone(s)

## N

National Tuberculosis Association, fiftieth anniversary, (editorials) 69 631-633  
Navajos, tuberculosis among, (editorials) 61 586, 591, 80 200-206  
Navy  
  streptomycin regimen study in, July 1946-April 1949, 60 715-754  
  tuberculin testing in, 62 518-524  
Necrosis  
  of basal nuclei, in thrombosis of cerebral vessels, (case reports) 61 247-256  
  caseous, protein and nucleic acid in, 77 106-119  
Needle biopsy *See* Biopsy  
Negro(es)  
  American, tuberculosis control among, 60 332-342  
  tuberculous pneumonia in, 60 343-353, 68 382-392  
Neomycin  
  activity on *M. tuberculosis* and other mycobacteria, 60 78-89  
  aerosol, in pulmonary tuberculosis, (Notes) 78 135-137  
  in clinical tuberculosis, 63 427-433  
  in experimental tuberculosis, 62 300-306, 345-352  
  failure as adjuvant to streptomycin in tuberculous meningitis, (case reports) 65 325-331  
  resistance, genetic studies of, 62 286-299  
Neonatal period, tuberculosis in, 77 418-422  
Neoplasm(s) *See* Tumors  
Neotetrazolium  
  chloride, in tubercle bacilli cultures, (Notes) 68 625-628  
  inhibition test, 77 662-668  
Nephrectomy, partial, for tuberculosis, 66 744-749  
Nervous system, central  
  isoniazid effect, 69 261-266, 759-762  
  isoniazid-iproniazid effects, 69 261-266  
Neuritis, peripheral  
  and isoniazid metabolism, 70 266-273  
  in isoniazid treated patients, (case reports) 70 504-508  
Neuroma *See* Tumors  
Neuropathy, peripheral, in tuberculous patients treated with isoniazid, (case reports) 68 458-461  
Neurotoxicity, of dihydrostreptomycin  
  effects of longer term therapy, 63 312-324  
  sulfate, 65 612-616  
New York City  
  tuberculosis deaths in, (Notes) 77 516-518  
  tuberculin testing, (Notes) 69 1057-1058

## Niacin

production of typical and atypical mycobacteria, 77 669-671, 675-680

## test

in differentiation of tubercle bacilli, (Notes) 79 810-812

in distinguishing mycobacteria, (Notes) 79 663-665

## Nicotinamide

activation, in acidic environments, *in vitro*, (Notes) 70 748-751

-pyrazinamide, intracellular activation, 74 718-728

therapy of lingual changes in tuberculous patients, 62 360-373

Nicotinic acid, in mycobacteria, metabolism of, 75 529-537

## Nitrogen

asparagine as source of, for growth of *M. tuberculosis*, 68 127-135

clearance, in ventilatory efficiency, 72 465-478

effect, on growth, riboflavin production and synthesis of pharmacologically active metabolite, 68 119-126

influence on antimicrobial activity, 67 503-508

metabolism, in nontuberculous patients receiving isoniazid, 68 207-211

Nitrous fumes, exposure to, 76 398-409

*Nocardia* See Fungi

*Nocardia asteroides* See Fungi

Nocardiosis See Mycoses

Node(s) See Lymph nodes, Scalene nodes

Nodule(s), pulmonary

found in community roentgenographic survey, 79 427-439

in histoplasmosis, surgical significance of, (case reports) 69 829-836

solitary, calcification in, (case reports) 74 106-111

Nontuberculous disease, isoniazid prophylaxis in, (correspondence) 78 485-487

Nontuberculous infections, immunity in, (editorials) 71 592-595

Nose, swab cultures in pulmonary tuberculosis, (Notes) 80 909-910

## NOTES

Actinomycetales, susceptibility to isoniazid, compared with other synthetic and antimicrobial antituberculosis agents, 67 261-264

adenitis, tuberculous, 23 cases treated with isoniazid alone, 74 136-141

adrenocortical hormones in experimental tuberculosis in adrenalectomized mice, 77 536-538

amino acid(s), study of

metabolism, with urine from tuberculous patients, 76 867-870

related to the problem of host resistance to tuberculosis, 66 378-380

amphotericin B

aerosol, innocuousness and possible therapeutic use, 80 411-412

determination of serum concentrations in man of, 77 1023-1025

antituberculosis drugs, mechanism of the combined effect, 78 121-126

autoclavable medium, semisynthetic, for a routine tuberculosis laboratory, 78 788-792

bacilli, acid-fast

atypical, an expanded schema, 80 434-437

chromogenic

classification and susceptibilities to chemotherapeutic agents, 76 697-702

from human sources, *in vitro* response to a number of antimicrobial agents on glycerol-blood agar medium, 72 119-122

nontuberculous

recovered from human sources, 76 683-691  
studies on, penicillin susceptibility, 75 675-677

wild-type, typical and atypical, titration of cord formation as a measure of pathogenicity of, 78 799-801

bacteriologic specimens, agitator for, 70 176-177

BCG

biologic activity of crude extracts of, 78 939-943

immunization, lack of circulating antibodies after, as assayed by the globulin titration technique, 78 793

and its isoniazid-resistant mutant in guinea pigs, comparative study of the vaccinating properties of, 75 656-658

new method of production, 64 698-701

present status of studies, 68 462-466

vaccination, in Republic of Panama, 67 522-525

vaccine

harvesting and dispensing apparatus for, 63 613-614

new method of counting viable organisms in, 79 816-817

viability, 63 714-716

influence of methods of preparation on, 64 695

vital staining method for the rapid estimation of the bacterial count, 78 785-787

## No'es, cont

- benzoyl para-aminosalicylic acid, biochemical aspects of metabolism of, 75 1003-1006
- breathing capacity, maximal, comparison of spirometric and Douglas Bag measurements, 79 253-255
- bronchograms, under hypnosis, 79 525
- bronchoscopy
  - in diagnosis and localization of bacteriologically positive tuberculous lesions, 73 586-588
  - sputum examination after, 77 716-718
- bronchspirometry, vital capacity in, 76 320-321
- calcium benzoyl PAS, 75 667-669
- Candida albicans*
  - and adjuvants, experimental sensitization of guinea pigs with, 76 692-696
  - incidence of, in sputum of tuberculous patients, 72 543-545
  - means for detecting *M. tuberculosis* on culture media, 75 836-840
- case finding, tuberculosis, in psychiatric hospitals, 79 537-540
- chemotherapeutic compounds, antituberculosis, decomposition of, with reference to susceptibility tests, 73 593-596
- chemotherapy
  - in chronic fibrocaceous pulmonary tuberculosis, relapse rates after, 71 302-304
  - in pulmonary tuberculosis, evaluation of
    - Part I High doses of isoniazid-PAS-pyridoxine, 78 773-778
    - Part II Daily streptomycin plus high doses of isoniazid-PAS-pyridoxine, 78 779-784
  - regimens employing isoniazid alone and in combination with intermittent streptomycin in tuberculosis, incidence of bacterial resistance encountered with, 67 106-107
- chronic bronchitis, some clinical, pathologic, and bacteriologic aspects, 75 340-342
- Coccidioides immitis*, sporulation of 3 strains of, inhibitory effect of peptone on, 74 147-148
- "coin" lesions of the lung, 73 134-138
- corticotropin, effects of decreasing dosages upon the course of ocular tuberculosis in the rabbit, (Notes) 69 1051-1053
- cortisone, effect
  - on electrophoretic patterns and the hemagglutination reaction in the course of childhood tuberculosis, 73 964-965
  - of minimal dose combined with a subeffective dose of dihydrostreptomycin on experimental guinea pig tuberculosis, 67 101-102
- C-reactive protein, in pulmonary tuberculosis, 74 464-467
- cycloserine
  - alone and in combination with other drugs in experimental guinea pig tuberculosis, 75 510-513
  - clinical, bacteriologic, and pharmacologic observations upon, 74 128-135
  - effect
    - on experimental tuberculosis in guinea pigs, 72 117-118
    - on growing and resting tubercle bacilli, 72 685-686
  - evaluation, with high dosage of isoniazid in chronic treatment-failure pulmonary tuberculosis, 80 269-273
  - isoniazid, in ambulatory treatment of active tuberculosis after failure of previous chemotherapy, 80 89-94
  - physiologic disposition of, in experimental animals, 74 802-806
  - psychologic side effects produced by, in treatment of pulmonary tuberculosis, 73 438-441
  - pyrazinamide, in treatment of pulmonary tuberculosis, 78 927-931
  - therapy, in tuberculosis in humans, 74 121-127
  - toxicity
    - considerations of, 75 514-516
    - and pharmacology, 74 972-976
  - viomycin, in treatment of pulmonary tuberculosis, 79 90-93
  - in vitro* action on *M. tuberculosis*, 72 236-241
- cystoscopes, studies on sterilization of, 76 909-911
- 4 4'-diaminodiphenyl sulfone, excretion products of, 72 123-125
- dihydrostreptomycin, purified, 73 776-778
- discharge, length of stay and criteria for, in a large tuberculosis center, 74 961-963
- drug therapy, effect of, upon survival of tuberculous patients, 74 968-971
- electrophoresis
  - serum protein paper patterns
    - and Middlebrook-Dubos titer in tuberculous children after BCG vaccination, 79 522-524
    - preliminary observation with use of, as an index of progress in the tuberculous patient, 76 892-895
    - of tuberculous patients presenting therapeutic problems, 75 999-1002
  - zone, in starch gels, report on Smithies Method in normal adults and in patients with tuberculosis, 78 932-933

## Notes cont

- emphysema, mediastinal, pathogenesis of, complicating therapeutic pneumoperitoneum, 76 897-898
- empyema, tuberculous, pH of, 67 103-105
- enzymes, use of, to aid filtration of oropharyngeal washes through membrane filter, 79 541
- S-ethyl-L-cysteine, clinical trial in pulmonary tuberculosis, 74 142-144
- ethyl-thio-formyl compound, with antituberculosis activity, 77 1017-1018
- fungi, investigation into the role of, in pulmonary diseases in India, 78 644-646
- glycerol, traces of zinc in, 74 145-146
- HeLa cells, growth characteristics of acid-fast microorganisms other than tubercle bacilli in, 80 744-746
- H<sub>1</sub> Intensity ultraviolet, effect of, for sterilization, 77 457-458
- hucnstarch
  - metabolic products of, 74 798-801
  - seromucoid (serum mucoprotein) values in patients undergoing therapy by, 78 131-134
- Histoplasma capsulatum*
  - and *Blastomyces dermatitidis* polysaccharide skin tests in humans, 80 264-266
  - challenge of *Macacus irus* with, 75 849-851
  - laboratory infection with, 72 690-692
- Histoplasmin
  - sensitivity
    - in Alaskan natives, 79 542
    - urban focus of, 79 83-86
- Histoplasmin H-42, dose of, for skin testing, 77 546-550
- histoplasmosis, problem of, in a military tuberculosis hospital, 75 833-835
- Hooke's law, application to the elastic properties of the lung of, 77 863-866
- hospital, best doctor in, 79 533-536
- immersion oil, as possible source of diagnostic errors, 63 717
- immunity, antituberculosis, elicited in mice by methanol extracts of tubercle bacilli, enhancing effect of adjuvants on, 73 781-784
- immunization, against tuberculous infection, difference in response of 4 strains of mice to, 80 753-756
- index cards, for clinical data on patients in a tuberculosis hospital, 70 903-906
- infancy, incidence of tuberculous infection in, 74 149-151
- iproniazid, side effects accompanying use of, 68 270-272
- isoniazid
  - antagonism of
    - by certain metabolites, 68 938-939
    - conditional, and other antibacterial agents, 68 280-283
    - by hemin, and the tuberculostatic action of, 69 469-470
  - antituberculosis action, isonicotinic acid hypothesis of, 77 364-367
  - bacteriotropic activity of, in the presence of certain other compounds, 78 802-805
  - concentrations
    - comparison of, in blood of people of Japanese and European descent, 78 944-948
    - in culture media, effect of inspissation and storage on, 75 678-683
    - low, reliability of a microbiologic assay technique for measuring, 75 992-994
  - cycloserine, report on the use of, in 84 cases of pulmonary tuberculosis, 79 87-89
  - effect
    - of the "anti-isoniazid" substance produced by mycobacteria on the chemotherapeutic activity *in vivo* of, 73 764-767
    - of barbiturates on the toxicity of, 66 100-103
    - of early administration on immunizing activity of normal BCG and isoniazid-resistant BCG in guinea pigs, 75 650-655
    - on growing and resting tubercle bacilli, 69 125-127
    - on growth of tubercle bacilli from pulmonary lesions, 79 518-521
    - of ketone compounds by the inhibition of growth of tubercle bacilli *in vitro*, 68 273-276
    - on the tuberculin test, 67 535-537
  - experiments, on the prophylaxis of a minimal tuberculous infection of guinea pigs with an intermittent regimen, 77 999-1004
  - and other hydrazine derivatives, production of fatty livers in rabbits by, 73 956-959
  - inactivation of, by Dubos medium, 68 284-285
  - ineffectiveness of, in modifying the phenomenon of microbial persistence, 76 1106-1109
  - iproniazid, effect on *Coccidioides immitis*, 69 538
  - liberation of peroxide in the breakdown of, 73 779-780
  - medication, acquired resistance and, 79 97-101

# Notes isoniaid, cont

- metabolism of
  - by *Mycobacterium tuberculosis* BCG, with reference to current theories of the mode of action, 78 806-809
  - use of a serum microbiologic assay technique for estimating patterns of, 75 995-998
- mode of action of, and role of trace metals in inhibition of bovine liver catalase by isoniaid, studies on, 77 501-505
- PAS salt of, studies of, in the treatment of tuberculosis, 78 637-643
- pyridovine, massive dose in chronic pulmonary tuberculosis, 78 474-477
- resistant cultures isolated from clinical specimens, virulence in guinea pigs of, a preliminary report on, 68 290-291
- serum concentrations in tuberculous patients, effect of certain aromatic amines on, 76 152-158
- streptomycin, antagonism of, in experimental infection of mice with *M. tuberculosis* H37Rv, 68 277-279
- therapy
  - cystlike cavities in pulmonary tuberculosis and, 69 1054-1056
  - experimental reinfection in arrested guinea pig tuberculosis and its behavior under, 79 246-250
  - high dose, further experience with single-drug (isoniazid) therapy in chronic pulmonary tuberculosis, 77 539-542
  - isoniazid serum concentrations and total hemoglobin and methemoglobin values in tuberculous patients on two dosage regimens, 68 286-289
- Ivalon sponge plombage, 78 478-484
- kanamycin, effect on *M. tuberculosis* *in vitro*, 78 138-139
- leprosy, murine
  - effects of kanamycin, streptovaricin, paromomycin, novobiocin, and ristocetin on, 79 673-676
  - evolution of, 79 805-809
- lymphadenopathy, scalene, postmortem study, 76 503-505
- lymphadenitis, tuberculous, cervical, X-ray therapy in management of, 74 641-644
- Madison sentence completion form, use in a small tuberculosis sanatorium, 74 964-967
- mycobacteria
  - asparaginase of, 70 920-921
  - atypical strains
    - drug susceptibilities of 20, as compared with 19 selected strains of, 76 497-502
  - isolation of, from healthy persons, 80 747-749
  - and others, determination of growth rates as a means of estimating optimal growth periods for comparative biochemical studies, 79 94-96
  - and typical, quantitative aspects of neutral red reactions of, 79 526-530
  - distinguished by the niacin test, 79 663-665
  - effect of glutamic acid derivatives on growth and inhibition of, 75 688-691
  - failure of a method for enzymatic digestion and concentration of pathogenic fungi and, from sputum, 76 896
  - new liquid synthetic medium for the cultivation of species, 80 267-268
  - oxidation-reduction dyes in the determination of virulence of
    - results with, 68 786-787
    - test tube modification of, *in vitro*, 66 99
  - spontaneity of gradual increase of streptomycin resistance in, 75 841-842
- mycobacterial cells, crude, further observations on the biologic activity of, 80 274-276
- Mycobacterium avium*
  - genetic consideration on isoniaid-resistance system of, 77 519-523
  - relationship between drug-resistance and growth phase of, 76 298-300
  - sulfathiazole-resistant, decrease of mutation rate to streptomycin resistance in produced by presence of sulfathiazole, 76 301-307
- Mycobacterium leprae*, separation of, from tissues by enzyme digestion, 74 152
- Mycobacterium paratuberculosis*, chemical constituents of, 77 712-715
- Mycobacterium ranae*, isoniaid-dependent strains of, 68 631-633
- Mycobacterium smegmatis*, intermediary metabolism of glucose by, 73 589-592
- Mycobacterium tuberculosis*
  - circulating levels of the "plasma factor" responsible for *in vitro* leukocyte cytolysis during sensitization of guinea pigs with, 79 244-245
  - cultivation of Bacille-Calmette Guérin strain of, 78 934-938
- cultures of
  - collection of sputum for, obtained during local anesthesia prior to bronchography and bronchoscopy, 74 977
  - colorimetric test for measuring catalase activity of, 71 305-307
  - positive, obtained by incubation beyond the

*Notes, Mycobacterium tuberculosis cont*

- normal 7- or 8-week period, 69 307-308
- preservation of, by freezing, 64 696-697
- detection of
  - in sputum by pepsin digestion and interface concentration with pentane, 75 148-152
  - trisodium phosphate transport-digestion method of processing sputum and gastric specimens for, 70 363-366
- drug susceptibilities of
  - on charcoal agar medium, 71 447-451
  - rapid method for determining, 78 111-116
- gamma irradiated, and *Brucella suis*, preliminary report on vaccines prepared from, 79 374-377
- growth of, from resected specimens under various atmospheric conditions, 70 910-911
- influence of the size of inoculum on susceptibility testing of, 72 390-392
- isolation of
  - comparative study in, on artificial media and embryonated eggs, 70 912-915
  - comparative study of culture and guinea pig inoculation in, from specimens of human source, 72 687-689
  - evaluation of chick yolk sac method as compared with conventional laboratory procedures for, 77 511-515
- primary
  - development of a rapid microculture technique for, 73 576-580
  - evaluation of blood bank blood agar medium for, from sputum and gastric contents, 71 762-764
  - use of Dubos type solid medium for, from human discharges, 64 318-321
- isoniazid resistant
  - atypical histologic aspects of pulmonary tuberculosis as related to attenuation or loss of pathogenicity of, 76 871-876
  - relation of pyrogallol peroxidative activity to, 75 670-674
- isoniazid susceptible and resistant strains, catalase and peroxidase activities, 79 669-671
- PAS resistant, observations on composition of bacterial population, 77 346-349
- pyrazinamide level of significant in vitro susceptibility of, on three different solid media 67 591-595
- selective activity of fluid thioglycolate medium for growth differentiation of atypical chromogenic mycobacteria,

- and saprophytic mycobacteria, 77 356-358
- streptomycin- and isoniazid-resistant strains, further observations on prevalence of, in patients with newly discovered and untreated active pulmonary tuberculosis, 74 293-296
- Vallée strain, immunizing properties of an isoniazid-resistant mutant, as compared with BCG observations in the mouse and guinea pig, 70 527-530
- Mycobacterium tuberculosis* H37R<sub>1</sub>, effects of mechanical agitation on the growth of, 79 813-815
- Mycobacterium tuberculosis* H37R<sub>1</sub>
  - development of leukocytic susceptibility to tuberculin in guinea pigs experimentally infected with, 76 888-891
  - preliminary observations on development of atypical (chromogenic) variants of, under influence of streptomycin-isoniazid *in vitro*, 78 921-926
  - studies of the catalase activity of, 80 257-258
- neomycin aerosol, results of clinical trial of, in treatment of pulmonary tuberculosis, 78 135-137
- pain, pleuritic, appraisal of theories, 69 634-635
- pancreas, in experimental tuberculosis, guinea pig inoculation via the intraperitoneal route, 78 794-798
- PAS
  - buffered tablets, blood concentration studies with, 72 543-547
  - conjugated, and ascorbic acid and other forms of PAS, studies of
    - comparison of 24 hour blood serum concentrations, 76 880-887
    - patient tolerance, 76 877-879
  - effect of, on silicate restorations (fillings) of teeth, 68 622-624
  - isoniazid, direct antithyroid action of, 71 889-891
  - resin complex, studies in absorption, serum electrolytes, and tolerance, 72 548-551
  - spectrophotometric determination of, and its acetyl derivative in human urine, 64 577-578
  - test, urine
    - detection in ambulatory tuberculous patients by, 79 672
    - simple paper strip, 80 555-556
  - therapy, prothrombin time during, 2000 determinations in 100 patients, 67 258-260
- para isobutyl benzaldehyde thiosemicarbazone clinical trial in series of tuberculosis, 65 799-802

Notes, para isobutoxybenzaldehyde thiosemicarbazone, cont

- failure, as an antituberculosis drug in man, 68 791-793
- in the treatment of pulmonary tuberculosis, 68 794-795, 796-798
- penicillin
  - as a decontaminant in cultures for tubercle bacilli from undigested sputum, 67 530-534
  - instability of, in Dubos media, 80 262-263
  - plasma, influence of tuberculosis on the methylene blue reduction time of serum and heat coagulation value, 70 907-909
- pleural effusions, tuberculous, age distribution of, 70 901-902
- pleural exudate, bacteriologic study of, following small resections for pulmonary tuberculosis, 73 773-775
- pneumothorax, artificial, induction of, 71 596-599
- polyoxyethylene ether (Triton WR 1339), failure of, to protect against tuberculin shock in guinea pigs, 79 382-383
- polyserositis, tuberculous, 80 259-261
- PPD, johnin and tuberculin, sensitization of cattle erythrocytes with, 77 177-180
- $\beta$ -Propylal- $\gamma$ -butylal-imine, new substance with inhibitory effect on *M. tuberculosis* var *hominis* H37Rv, 76 1094-1096
- pulmonary resection
  - methods of drainage after, 69 636-637
  - in the rabbit, 73 123-127
  - United States Veterans Administration-Armed Forces cooperative studies of tuberculosis results, 1952-1955, 73 960-963
- pyrazinamide
  - antituberculosis activity *in vitro* and in the guinea pig, 70 367-369
  - cycloserine, in treatment of pulmonary tuberculosis, 76 1097-1099
  - isoniazid
    - in patients with previous isoniazid therapy, 75 846-848
    - therapy, occurrence of hyperuricemia during, 74 289-292
    - in tuberculosis results in 58 patients with pulmonary lesions one year after the start of therapy, 70 713-747
    - in low dosage, in combination with isoniazid or PAS in the treatment of pulmonary tuberculosis, 79 102-104
    - nicotinamide, activation in acidic environments *in vitro*, 70 748-754
    - pyridoxine
      - isoniazid
        - antagonism, delayed appearance of, *in vivo*, 76 1100-1105
        - concurrent administration of, 74 471-473
      - radioactive gold (Au<sup>198</sup>)
        - lymphatic drainage of pericardial space in dogs, as determined by studies with, 76 906-908
        - lymphatic drainage of pleural space in dogs, as determined by studies with, 75 145-147
    - reserpine, in treatment of tuberculous mental patients, 74 457-461
    - riboflavin, as an indicator of isoniazid ingestion in self-medicated patients, 80 415-423
    - roentgenographic duplication, solarized, 75 139-144
    - roentgenography, mass, results among immigrants into Israel, 69 837-840
    - Salizid®-isoniazid, antimicrobially active concentration in blood, 74 796-797
    - sarcoidosis
      - geographic distribution of, 70 899-900
      - ineffectiveness of isoniazid-isoniazid in therapy of, 67 671-673
      - secondary factors involved in the etiology of 71 459-461
    - serum albumin, factor preventing inhibition of propagation of D-29 mycobacteriophage by Tween® in, 80 443-444
    - serum enzymes in pulmonary tuberculosis, glutamic oxalacetic transaminase and glutamic pyruvic transaminase, 79 251-252
    - serum lipase, studies, 78 117-120
    - sputum
      - examination
        - collection and selection, 76 671-674
        - search for elastic tissue, 76 675-678
        - search for fungal spores, 76 679-682
      - tuberculous, preparation for membrane filter filtration, 77 1019-1022
    - streptomycin
      - isoniazid-PAS, in treatment of pulmonary tuberculosis, 73 117-122
      - susceptible infections, control study of comparative efficacy of isoniazid, streptomycin-isoniazid, and streptomycin-PAS in pulmonary tuberculosis therapy
        - report on 20-week observations on 300 patients with, 67 108-113
        - report on 28-week observations on 649 patients with, 67 539-543
        - report on 40-week observations on 583 patients with, 68 264-269



*Notes, etc.*

streptomycin

alone, in treatment of active pulmonary tuberculosis, 80 423-427

alone, and with isoniazid, influence of in experimental tuberculous infection in animals, and some clinical observations 75-752-675

-isoniazid

controlled clinical trial, 80 757-759

in treatment of pulmonary tuberculosis, 80 424-425, 426-427 431-433

isurine, in treatment of tuberculosis in guinea pigs 74-553-559

thio-carbanilide-isoniazid, clinical evaluation of, in treatment of pulmonary tuberculosis, 80 550-553

thio-carbanilide ST 1976, pilot study of in human pulmonary tuberculosis, 74 468-470

thoracoplasty, constrictive suture (Paulino), 71-832-833

tranquilizing drugs, effect of, on non-isolated tuberculous patients, 73-127-130, 79-531-532

trihydroxy-uronic-propyl thio-carbonyl effect on nature resistance to tuberculosis, 73 434-437

Trilon A-20-1 4-dimethyl-7-isopropyl-rigolo-decapentane, experiments on the mechanism of action of 75-584-587

Trilon WR 1039, and malachite green, use in charcoal media for tubercle bacilli, 71-834-837

tubercle bacilli

cultivation, inpassation of egg media for, 73-133-141

cultures

blowing phenomenon a source of contamination in 80-295-297

experiments with a new method for, 69-334-375

Sorn-clot technique for isolation of, from pleural exudates, 80 438-440

filter paper technique for the early detection of macrocolonies of 70-216-219

recently isolated, isoniazid susceptibility, catalase activity, and guinea pig virulence of, 73 768-772

from reserated lung lesions, comparison of bovine albumin and physiologic saline as diluents of tissue homogenates in the recovery of tubercle bacilli by culture and animal inoculation, 70-570-572

use of neotetracycline chloride in, 68-625-628

in vitro method of, the chamber method, 72-233-237

cytology, phase contrast studies of changes produced in during growth, 73-274-285

detection of

rapid evaluation of egg embryo as indicator procedure for 75-215-310

Trilon-malachite green-charcoal agar medium for 75-338-339

dilutions

isolation of potency of 72-125-128

a second report 74-227-233

drug-tests and rapid detection in sputum by slide cultures 75-231-233

effects of various methods of extraction on the spectroscopical infection-enhancing properties of 77-1024-1029

electron-microscope and phase contrast studies of effects of PAS isoniazid, and streptomycin, 73-295-300

human, differentiation of, from streptococcal and bacillary modification of the medium test using Tween<sup>8</sup>-albumin liquid medium 73-510-512

isolation relative efficacies of chick embryo and standard ATS media in from human sputum 73 708-715

isoniazid-resistant

catalase activity of a preliminary report 69 471-472

observations on the pathogenesis of the lesions caused by, in the guinea pig 74-553-557

regression of tuberculous lesions in guinea pigs infected with, 70-531-532

study of the virulence of in guinea pigs and mice, a preliminary report, 69 454-458

PAS-resistant genetic considerations of the mechanisms involved in, 73-371-373 within pulmonary lesions effect of degree of healing upon persistence of 72-283-339

in the rabbit

given cortisone possible role of humoral factors in enhanced growth of 77-522-535

nature of virulence of human and bovine strains 67-235-236

rapid microculture method for isolation of, 75-1007-1008

from reserated pulmonary lesions influence of quartz on the recoverability of, 71-375-383

respiratory quotients of, at low oxygen tension, 67-562-570

*Notes, tubercle bacilli, cont*

- ring method, for analyzing effect of serum on growth of, *in vitro*, 77 524-528
- and saprophytic mycobacteria, simple technique for differentiation of, 74 958-960
- significance of delayed emergence of, 75 506-509
- in sputum, assay of tuberculous contamination on eating utensils of patients with, 74 462-463
- suspensions, rapid chemical test for total viability of, 66 95-98
- tuberculin shock in mice infected with, 68 629-630
- in tuberculous lesions, use of quartz dust for challenging the viability of, 69 841-842
- virulent, mixed with BCG, resistance of guinea pigs to infection with small numbers of, 72 539-542
- tuberculin
  - effect on oxygen utilization of blood and of splenic tissue from tuberculous and normal guinea pigs, 73 581-585
  - formation, by washed tubercle bacilli, in citrate solution, 67 526-529
  - hypersensitivity
    - cutaneous, use of tuberculin-treated erythrocytes as antigen in eliciting, 64 322
    - study in 510 patients hospitalized for active pulmonary tuberculosis, 74 474
  - patch test, survey among school-age children in Liberia, 67 665-668
  - purified fraction from unheated cultures, in testing BCG-vaccinated subjects, preliminary report, 69 300-303
  - reaction, intracutaneous, effect of topical hydrocortisone acetate ointment at site of, 79 666-668, 80 587-589
  - testing
    - pilot study for case finding in a general hospital, 79 378-381
    - studies in New York City, 69 1057-1058
- tuberculosis
  - antimicrobial therapy, U S Public Health Service cooperative investigation of, report on 32-week observations on combinations of isoniazid, streptomycin, and PAS, 70 521-526
  - bacteriologic media, elimination of precleaning cage laid hens' eggs in preparation of egg fluid, 79 677
  - comparison of roentgenographic and surgical findings in, 71 452-456
  - cost of, estimate for fiscal 1956, 77 172-176
  - drug susceptibility testing in, 77 350-355
  - experimental
    - in guinea pigs, effects of phagocytic stimulation on, 73 442-443
    - in mice, control of, by intermittent administration of streptomycin, viomycin, isoniazid, and streptomycin-cyclidene isonicotinyl hydrazine, 68 292-294
    - short-term therapy, 77 867-868
  - miliary and meningeal, in childhood, in New York City, 77 359-363
  - mortality
    - current analysis of, in New York City, 77 516-518
    - in Puerto Rico since 1950, 70 1099-1101
    - rates, among World War II veterans (a screened population) for the years 1953 and 1954, further report on, 73 966
  - pulmonary
    - problems in surgical management of, 76 902-905
    - rapid mouse test for diagnosis of enhancement of experimental tuberculosis in mice by hog gastric mucin, 77 1005-1011
    - preliminary studies with patients' specimens, 77 1012-1016
    - results of an international survey of, 73 123-133
    - surgical pathology of isoniazid-treated, 68 144-149
    - susceptibility, of normal and immunized mice, relationship of sex to, 80 750-752
  - tuberculous cavities, giant cells lining healing, 78 140-144
  - tuberculous infection, during academic studies, 76 308-314
  - tuberculous patient, uncooperative, compulsory isolation of, experience in the state of Georgia, 77 506-510
  - tuberculostatic agent, present in animal tissues, 63 119
  - tuberculostatic factor, in normal human urine, 73 967
  - ultrafiltration, improved apparatus, 63 718-720
  - vaccination, antituberculosis, in guinea pig, with nonliving vaccines, 77 719-724
  - vaccine, irradiated, trials with, 75 987-991
  - viomycin, in the re treatment of pulmonary tuberculosis, 72 843-845
  - X-ray viewer, new multipurpose, magnifying, 63 788-790
  - Zephiran®, use of, in the isolation of *M. tuberculosis*, 74 284-288
- Novobiocin, 76 272-278
  - in murine leprosy, 79 673-676

- Nuclei, and mitochondria in *M tuberculosis*,  
67 59-73
- Nucleic acid in caseous necrosis, 77 106-119
- Nucleinemia, (correspondence) 67 515-516
- Nurse(s)  
pathogenesis of tuberculosis in, 60 305-331
- student, tuberculosis control in, 73 868-881
- Nutrition  
in tuberculosis, 62 58-66, 64 381-393  
in adolescents, 74 (Supplement, August 173-183)
- Nydrasid® See Isoniazid
- Nystatin in experimental coccidioidomycosis,  
72 64-70

## O

## OBITUARIES

- Adcock, John D , 69 650
- Alexander, John, 71 326-329
- Anglin, George Chambers, 60 388
- Aronson, Joseph David, 79 695
- Barrier, Leonidas F , 79 394
- Baum, Felix, 78 490
- Bellinger, Grover C , 75 861
- Bernard, Richard Charles, 78 148
- Biggs, Ray Hoyt, 77 371-372
- Boswell, Henry, 78 146
- Brady, Edwin Herms, 79 394
- Bray, Harry Alfred, 75 859-860
- Brueckner, Harold H , 120
- Brumfiel, Daniel M , 79 396
- Bruno, Alexandre, 70 544
- Brzozowski, Grover S , 79 394
- Byrne, Ethel, 78 493
- Cahill, John D , 78 147
- Calhoun, Orange V , 70 187
- Cheifetz, Irving, 69 654
- Chesley, Albert J , 74 165-166
- Clemens-Meyer, Henry, 78 494
- Clovis, E E , 78 147
- Cohen, Louis, 67 552
- Collins, Loren L , 70 188
- Cooley, Samuel S , 79 118
- Cox, Seth, 66 123
- Craig, Frank Ardary, 80 921-922
- Creelman, Prescott Archibald, 78 490
- Cutler, Jacob W , 78 147
- Dahlstrom, Arthur W , 80 120
- Davis, John Dwight, 69 653
- Dawson, Francis P , 78 491
- Douglas, Bruce H , 60 812
- Duggeli, Otto, 78 494
- Ferlano, Frank, 69 654
- Frost, William Dodge, 76 326-327
- Giese, Charles Oscar, 75 352
- Goodrich, Benjamin E , 70 187
- Gray, Frederick James, Jr , 79 118
- Guild, Cameron St Clair, 71 330-331
- Hatfield, Charles James, 66 118-120
- Hendricks, Charles McChristie, 70 188
- Heusinkveld, David W , 73 310
- Holmes, Fred Gooding, 73 312
- Jaffin, Abraham Ezra, 67 398
- Jaso, James, 78 491
- Jegi, Henry A , 70 543
- Joannides, Minas, 67 551
- Karcher, James Franklin, 69 654
- Kaufman, Charles J , 74 819
- Knob, Perry McGregor, 78 493
- Kolb, Paul Edwin, 69 653
- Lange, Horst, 79 395
- Laroche, Armand, 78 493
- Leopold, Simon Stein, 78 490
- Lerrigo, C H , 74 164
- Logie, Arthur Jones, 67 398
- Lubin, Solomon S , 78 491
- Lyman, David Russell, 75 860-861
- McConkey, Mack, 80 121
- McCorkle, Robert G , 70 188
- Mantz, Herbert L , 69 651
- Marcley, Walter J , 74 164-165
- Marcy, C Howard, 80 452-453
- Mariette, Ernest S , 63 615
- Mattill, Peter Milton, 78 492
- Medlar, Edgar M , 74 818
- Metcalf, Walter Bradford, 75 862
- Milham, Claude Gilbert, 78 148
- Miller, James Alexander, 59 467-468
- Moorman, Lewis Jefferson, 71 329-330
- Moreland, Andrew John, 76 927
- Morgan, Hiram Burnard, 78 492
- Mulky, Carl, 70 543
- Nissler, Christian William, 69 653
- Novy, Frederick George, 80 922-923
- Nylander, P E A , 75 353
- Ordway, William Herbert, 74 163-164
- Pattison, Harry A , 76 327
- Petroff, Strachimer A , 60 387-388
- Pierce, Eugene B , 73 311
- Puckett, Carl, 78 146
- Randel, Henry A , 73 311
- Ratner, Bret, 78 148
- Ringer, Paul, 67 398-399
- Rogers, Edward James, 66 122-123
- Roll, Lewis Robert, 69 653
- Roosth, Harold, 77 371
- Rosencrantz, Esther, 66 121-122
- Ross, Will, 66 120-121
- Sabin, Florence Rena, 69 649
- Schantz, John Philip, 79 394
- Schindler, John Albert, 78 149
- Schoenfeld, Siegfried, 70 544
- Schultze, Joseph H , 70 187
- Seldon, Frank G , 79 395
- Shepard, Marguerite D , 78 146

*Obituaries, cont*

- Siegal, William, 75 352-353  
 Simpson, Sutherland Eric R, 70 544  
 Sloan, E F, 79 395  
 Smith, Roy Kenneth, 77 372  
 Soparkar, Manmohandas B, 67 399  
 Steinbach, Maxim, 62 449  
 Stone, Arthur Kingsbury, 67 399  
 Stone, Moses J, 67 551-552  
 Stucky, George C, 66 122  
 Terrill, Frank I, 78 149  
 Test, William Brantingham, 78 147  
 Thayer, Lyman I, 80 120  
 Thearle, William Henry, 70 543  
 Thompson, Ira F, 70 543  
 Thompson, Rollin David, 75 862-863  
 Trembley, Charles Carthers, 78 148  
 Trimble, Harold Guyon, 76 711-712  
 Trudeau, Francis B, Sr, 74 819  
 Vicente-Mastellari, Amadeo, 75 353-354  
 Walker, Arthur Meeker, 73 790  
 Walker, William Dunn, 79 394  
 Watkins, William Warner, 74 650-651  
 Wilkinson, Michael R, 70 544  
 Wilson, John Nants, 66 123  
 Wood, Lawrence E, 80 543-544  
 Wright, Louis Tompkins, 67 551  
 Zahn, Daniel W, 74 650
- Obesity**  
 maximal breathing capacity in, (Notes) 80 902-903
- Occupational therapy and rehabilitation in tuberculosis hospitals, (correspondence)** 79 680, 80 445-447
- Ocher workers, silicosis in, (case reports)** 77 839-847
- Ocular tuberculosis** *See* Tuberculosis
- Oleothorax, followed by intrathoracic cysts, (case reports)** 66 601-604
- Omental spreads, changes following inoculation of tubercle bacilli in guinea pigs, 73 362-377**
- Omentum**  
 guinea pig, as index of antimicrobial effectiveness, 68 583-593  
 vs pancreas in experimental tuberculosis, (correspondence) 80 445
- "Open-healing" of cavities, 73 944**  
 persistent, during chemotherapy, 75 242-258  
 tuberculous, 75 223-241
- Open negative syndrome, (correspondence)** 76 508-509  
 clinical studies, 78 725-734  
 home care in, 77 764-777  
 surgical and nonsurgical treatment, 75 538-552
- Ornithosis, antibodies in, tetracycline influence on, 74 566-571**

- Oropharyngeal region, enzymes to aid filtration of washes from, (Notes)** 79 541
- Osteoarthropathy, hypertrophic, and interstitial pulmonary fibrosis, (correspondence)** 79 543
- Osteochondritis, in mediastinal tuberculosis, (case reports)** 79 238-243
- Osteogenesis imperfecta, and tuberculous pleurisy, (case reports)** 67 514-516
- Oxidation, in relation to tubercle bacilli virulence, 64 520-533**
- Oxidation-reduction dye test, for mycobacterial virulence, 69 599-603, (correspondence)** 66 382-383, (Notes) 68 786-787
- Oximeter**  
 direct-writing ear, in respiratory function tests, 74 511-532  
 test, in diagnosis of emphysema, 80 705-715
- Oxygen** *See also* Pulmonary function  
 arterial, lack measured by oxygen tension, 79 315-322  
 breathing, in respiratory acidosis, 77 737-748  
 diffusing capacity, during exercise, 80 806-824  
 and glucose, in autolysis of *M tuberculosis*, 73 907-916  
 tension gradient, alveolar-arterial, in pulmonary disease, 69 71-77  
 test, single-breath, terminal rise in, 75 745-755
- Oxytetracycline**  
 antituberculosis activity, 72 367-372  
 bactericidal action on extracellular and intracellular tubercle bacilli, 67 322-340  
 -streptomycin in pulmonary tuberculosis, 66 534-541, 69 58-70  
 tuberculostatic activity of, 63 434-440

**P**

- P<sup>32</sup>-labeled tubercle bacilli, virulence of, 79 738-745**
- PABA** *See* Para aminobenzoic acid
- Pain**  
 pleuritic, (Notes) 69 634-635  
 threshold in tuberculous patients, 66 449-456
- Panama**  
 BCG vaccination, (Notes) 67 522-525  
 coccidioidin sensitivity in, 63 657-666
- Panarteritis, with sarcoidosis, (case reports)** 60 236-248
- Pancreas**  
 in experimental tuberculosis, (Notes) 78 794-798  
 vs omentum in experimental tuberculosis (correspondence) 80 445
- Pancreatic desoxyribonuclease, in pulmonary abscesses, 76 1-21**
- Pancreatin-quaternary ammonium compounds in sputum cultures, 72 98-106**

*Pancreatin quaternary ammonium cont*

treatment of urine and gastric lavage specimens  
for cultivation of *M. tuberculosis*,  
71 616-621

Pancreatitis and other diseases, pleural fluid  
amylase in, 79 606-611

Paper electrophoresis *See* Electrophoresis

Papilloma *See* Tumors

Papillomatosis *See* Tumors

Para aminobenzoic acid

in increase of bacteriotropic potencies of isoniazid, (correspondence) 78 949-951

isoniazid action in presence of, (correspondence)  
76 706-707

Para aminosalicylic acid

absorption of the sodium salt from the rectum,  
63 213-219

allergic reaction, 65 235-249

fatal, (case reports) 69 451-454

antithyroid action, (Notes) 71 889-891

-ascorbate

in blood serum concentrations, (Notes)  
76 880-887

patient tolerance of, (Notes) 76 877-879

-benzoyl-PAS

inhibiting isoniazid inactivation in man,  
80 26-37

metabolism, biochemical aspects, (Notes)  
75 1003-1006

in blood and urine, spectrophotometric determi-  
nation, 76 1071-1078

buffered, in blood concentration studies, (Notes)  
72 543-547

C<sup>14</sup>-labeled, and isoniazid, 75 71-82

calcium-calcium benzoyl, tolerability of, 79  
351-356

calcium salt, patient tolerance for, (Notes)  
66 619-620

causing anaphylactic shock, (case reports)  
77 492-495

cholangiolitic hepatitis due to, (case reports)  
76 132-139

concentrations

in blood, effect of probenecid on, 66 228-232

effect of light on, assay of, 75 93-98

studies, (Notes) 72 543-547

determination

in body fluids, 76 852-861

spectrophotometric, in human urine, (Notes)  
64 577-578

effect

on silicate restorations (fillings) of teeth,  
(Notes) 68 622-624

on tubercle bacilli, phase contrast and elec-  
tronmicroscopic studies, (Notes)  
73 296-300

goitrogenic, (case reports) 69 458-463

granules, shellac coated, absorption of, (cor-  
respondence) 76 159-160

ingestion test, (correspondence) 71 810

intravenous administration, (correspondence)  
60 385-386

-isoniazid

compared with pyrazinamide-isoniazid,  
73 701-715

effect on thyroid function, 80 845-848

in original chemotherapy of noncavitary  
pulmonary tuberculosis, 80 641-647

single daily dose, 78 749-752

streptomycin, combinations of, therapeutic  
and toxic effects, 69 1-12

in tuberculous sinuses and fistulas, 68 535-540

limitations of knowledge of, (editorials) 76 491-  
496

Löffler's reaction to, (case reports) 70 171-175

methemoglobinemia and hemolytic anemia  
following ingestion of, (case reports)  
76 862-866

paired with other drug combinations, 80 627-640

plasma concentrations

influence of *p* (di *n* propylsulfamyl) benzoic  
acid on, 61 862-867, 64 448-452, 453-  
460

with potassium iodide in chronic fibroid pul-  
monary tuberculosis, 64 77-80

preparations, in tuberculosis, 78 899-905

and probenecid, effect on blood, 66 228-232

-pyrazinamide, in pulmonary tuberculosis,  
70 413-422

reactions, (case reports) 72 833-849

simulating tuberculous meningitis, (case  
reports) 64 682-685

-resin complex, (Notes) 72 548-551

-resistant tubercle bacilli, 75 608-617, (Notes)  
77 346-349

genetic considerations of mechanisms in-  
volved in, (Notes) 79 371-373

isoniazid in, 66 477-485

salt

-isoniazid, in tuberculosis, (Notes) 78 637

severe hypersensitivity to, (case reports)  
78 462-467

shock, near fatal, and Guillain-Barrès syn-  
drome from, (case reports) 69 455-457

sodium salt in tuberculosis, 64 557-563

in sputum, 71 860-866

effect on culture of tubercle bacilli, 68 42-47

-streptomycin

aplastic anemia following use, (case reports)  
68 455-457

compared with isoniazid and streptomycin-  
isoniazid in pulmonary tuberculosis,  
(Notes) 67 108-113, 68 264-269

-corticotropin, in pulmonary tuberculosis,  
66 542-547

# *Streptomycin*

- effect on tubercle bacilli *in vitro* and *in vivo*, 59 551-561
- ethylmide in pulmonary tuberculosis and systemic blastomycosis, (case reports) 68 615-621
- in pulmonary tuberculosis, (Notes) 72 212-214
- sustained action tablets, blood concentrations with, (Notes) 77 181-188
- therapy, prothrombin time determinations during, (Notes) 67 258-260
- toxic reaction to, accompanied by leukopenia and lymphocytosis, (case reports) 60 821-828
- in tuberculosis
  - experimental
    - in guinea pigs
      - combined with dihydrostreptomycin alone or with Tibione, 63 339-345
      - single and double daily doses of, 78 753-759
    - in mice, inability to delay emergence of streptomycin resistant tubercle bacilli in, 62 156-159
  - extrapulmonary, 61 613-620
  - intestinal, 61 621-612
  - pulmonary, 61 226-246, 597-612, 613-620, (Notes) 73 117-122
    - dosage forms, 62 610-617
    - febrile reactions, 61 613-617
    - hypopotassemia and hyponatremia during treatment, 66 357-363
    - intermittent regimens, combined with streptomycin in treatment of, 63 295-311
    - with pyrazinamide or isoniazid, (Notes) 79 102-104
  - urine test for detection in ambulatory tuberculous patients, (Notes) 79 672
- Para-(di *n* propylsulfamyl) benzoic acid, influence on PAS plasma concentrations, 61 862-867, 64 448-452, 453-460
- Para ethylsulfonyl benzaldehyde thiosemicarbazone *See* Thiosemicarbazones
- Para formylacetanilide thiosemicarbazone *See* Thiosemicarbazones
- Para isobutoxy benzaldehyde *See* Thiosemicarbazones
- Paralysis
  - of phrenic nerve *See* Phrenic nerve
  - recurrent, of laryngeal nerve, as complication of pulmonary tuberculosis, 65 93-99
  - of vocal cords, 73 52-60
- Paratubercle bacilli, skin reaction to products of, 79 731-737
- Parkinson's syndrome, dyspnea in, 78 682-691
- Paromomycin, in murine leprosy, (Notes) 79 673-676

PAS *See* Para aminosalicylic acid

## Pathogenicity

- loss or attenuation, in pulmonary tuberculosis, during prolonged chemotherapy, (Notes) 76 871-876
- of streptomycin dependent tubercle bacilli, 63 96-99

## Pathogenesis

- of emphysema, 62 15-57
- of extrapulmonary tuberculosis, 62 (Supplement, July 48-67)

Pathology of tuberculous meningitis, effect of streptomycin on, 61 171-184

## Patient(s)

- and physician, 62 (Supplement, July 68-75)
- tuberculous
  - behavior rating, 70 483-489
  - education for, 70 190-497
  - evaluation of attitude, 67 722-731
  - leaving hospital against advice, personality characteristics, 67 432-439

Paulino procedure, (Notes) 71 892-893

Peliosis hepatis, 67 385-390

Pemoline type case conference, consecutive, manual for, 79 258-263

Penal institutions, pulmonary tuberculosis in, 61 51-56

## Penicillin

- as decontaminant in cultures for tubercle bacilli from undigested sputum, (Notes) 67 530-534
- instability, in Dubos media, (Notes) 80 262-263
- susceptibility
  - of human acid fast bacilli, nontuberculous, (Notes) 75 675-677
  - and virulence, in *M. tuberculosis*, 80 849-854
- in wound infection after thoracoplasty, 61 346-352

Pentane, concentration of *M. tuberculosis* in sputum, (Notes) 75 148-152

Pepsin digestion, of *M. tuberculosis* in sputum, (Notes) 75 148-152

Peptic ulcer *See* Ulcers

Peptone, inhibition of sporulation of *C. immitis* by, (Notes) 74 147-148

## Periarteritis

- nodosa, lung cavitation in, (case reports) 74 624-632
- with sarcoidosis, (case reports) 60 236-248

## Pericarditis

- chronic, biopsy in, 75 469-475
- and lymphatic drainage, (Notes) 76 906-908
- in mediastinal tuberculosis, (case reports) 79 238-243
- in tuberculosis sanatorium, 76 636-642
- tuberculous, 59 650-655
- streptomycin in, 59 656-663

- Personality**  
 and behavior in hospitalized tuberculous patients, 76 232-246  
 characteristics, of tuberculous patient who leaves hospital against advice, 67 432-439
- Peroxidase**  
 activities of isoniazid susceptible and -resistant strains of *M. tuberculosis*, (Notes) 79 669-671  
 catalase and isoniazid relation in mycobacteria, 75 62-70
- Peroxide**  
 in breakdown of isoniazid, (Notes) 73 779-780  
 formation in media for isoniazid-resistant *M. tuberculosis*, 75 476-487
- pH**  
 effect, on streptomycin susceptibility of resistant strain of *M. tuberculosis*, 62 91-98  
 of tuberculous empyema, (Notes) 67 103-105
- Phagocyte(s)**  
 in experimental tuberculosis, stimulation in guinea pigs of, (Notes) 73 442-443  
*in vitro*, effect of tubercle bacilli on migration of, 59 562-566
- Phagocytosis of *M. smegmatis* and *M. tuberculosis***  
 stained with indicator dyes, 74 552-565
- Phase contrast studies**  
 in cytology of tubercle bacilli, (Notes) 73 294-295  
 of effect of PAS, isoniazid, and viomycin on tubercle bacilli, (Notes) 73 296-300
- Phenazine(s) (B663)**  
 antituberculosis activity, 80 871-875  
 in experimental tuberculosis, 78 62-73
- Philadelphia (Pennsylvania), rehabilitation of tuberculous in,** 62 190-203
- Photofluorography, radiation hazard in, method to reduce,** 77 923-930
- Photoroentgenography of chest, in Baroness Erlanger Hospital, Chattanooga (Tennessee),** 60 377-382
- Photosensitivity of *M. tuberculosis*,** 71 112-125
- Phreniclasia**  
 complications and sequelae, 60 168-182  
 in pulmonary tuberculosis, 60 168-182, 183-188
- Phrenic crush, pulmonary function after,** 71 676-692
- Phrenic nerve**  
 interruption  
     followed by gastric dilatation, (case reports) 62 331-332  
     preceding linear basal atelectasis, 65 88-92  
     in pulmonary tuberculosis, 60 168-182, 183-188
- paralysis  
         for pulmonary tuberculosis, pneumoperitoneum with, 61 323-334  
         so called temporary, permanence of, 63 81-84
- Phthienoic acid** *See* Acids
- Phthisiotherapy, urgent indications for chemotherapy as, (correspondence)** 74 153-155
- Phthisis** *See* Tuberculosis, pulmonary
- Physical activity**  
 and bed rest on recovery from pulmonary tuberculosis, 75 359-409  
 energy cost during, 71 722-731
- Physical therapy** *See* Therapy
- Physician(s)**  
 and patient, 62 (Supplement, July 68-75)  
 on ward, evaluation by patients, (Notes) 79 533-536
- Pine pollen, failure to develop sarcoidosis after oral ingestion of, (correspondence)** 80 760
- Pilot ward study of air hygiene in tuberculosis,** 75 420-431
- Plasma** *See also* Blood  
 concentrations, effect of probenecid on, 64 448-452, 453-460  
 electrolytes, effect of viomycin on, 68 541-547  
 heat coagulation value, tuberculosis influence on, (Notes) 70 907-909  
 viscosity, in pulmonary tuberculosis, 69 595-598  
 "Plasma factor," circulating levels, in leukocytolysis in guinea pigs sensitized with *M. tuberculosis*, (Notes) 79 244-245
- Plastic reconstruction of trachea and bronchi,** 64 477-488
- Pleura**  
 diffuse malignant mesothelioma of, (case reports) 78 268-273  
 endothelioma, 63 150-175  
 parietal  
     needle biopsy of, in tuberculosis, 78 17-20  
     and visceral, lymphatics as drainage for, 79 52-65  
 pain in, theories appraised, (Notes) 69 634-635  
 Pleural effusion *See* Effusion
- Pleural exudate, after resection, (Notes)** 73 773-775
- Pleural fluid amylase in pancreatitis and other diseases,** 79 606-611
- Pleural tent in pulmonary resection,** 73 831-852
- Pleurisy**  
 with effusion, pathology of, 71 473-502  
 exudative, functional prophylaxis in, 66 134-150  
 tuberculous  
     with effusion, 62 314-323  
     in children, 77 271-289  
     modified bed rest in, 67 421-431

- Pleurisy tuberculous cont*  
 and osteogenesis imperfecta, (case reports)  
 67 514-516  
 primary, with effusion, antimicrobial therapy  
 in, 74 897-902
- Plombage**  
 Ivalon sponge, (Notes) 78 478-484  
 Lucite  
 ball, extraperiosteal, 68 902-911  
 fatal asphyxia from, (case reports) 61 422-425
- Pneumatosis cystoides intestinalis**, (case reports)  
 72 373-380
- Pneumocele(s)**  
 abdominal, following artificial pneumo-  
 peritoneum, (case reports) 60 520-523  
 diaphragmatic, in therapeutic pneumoperi-  
 toneum, 69 745-753  
 scrotal, during pneumoperitoneum, (case re-  
 ports) 74 622-623
- Pneumococcosis and tuberculosis**, 3,3',5 triodo-  
 L-thyronine in survival time of mice,  
 79 339-343
- Pneumoconioses**  
 anthracite coal miners (100)  
 with pulmonary complaints, respiratory gas  
 exchange studies in, 61 201-225  
 with respiratory complaints, pulmonary  
 emphysema and ventilation measure-  
 ments in, 59 270-288
- anthracosilicosis**  
 cavitation in, 71 544-555  
 tuberculosis in, 65 24-47
- beryllium**  
 case registry  
 establishment of, (correspondence) 68 941-  
 942  
 at Massachusetts General Hospital, (cor-  
 respondence) 72 129-132  
 compounds, granulomatosis following ex-  
 posure to, 60 755-772, 62 29-44,  
 65 142-158, 74 533-540  
 poisoning, and sarcoidosis, 74 885-896  
 workers, dyspnea in, 59 364-390
- Caplan's syndrome**, (case reports) 78 274-281  
 from diatomaceous earth, coalescent lesion of,  
 77 644-661
- dusts**, industrial, individual susceptibility to,  
 62 (Supplement, July 13-21)
- granulomatosis**  
 pulmonary  
 from beryllium, 74 533-540  
 in beryllium workers, dyspnea in, 59 364-  
 390  
 chronic, in beryllium workers, 62 29-44  
 diffuse, after exposure to beryllium, 60 755-  
 772, 65 142-158
- quartz dust**  
 for challenging viability of tubercle bacilli  
 in tuberculous lesions, (Notes) 69 841-  
 842  
 in demonstration of viable tubercle bacilli  
 in resected lesion after chemotherapy,  
 (Notes) 71 144-145  
 effect on recoverability of tubercle bacilli  
 from resected pulmonary lesions,  
 (Notes) 71 308-313  
 in experimental silicosis in guinea pigs, 69 766-  
 789  
 inhalation of, influence on tuberculous in-  
 fection by BCG, H37Ra, and *M*  
*marinum*, 69 763-789
- silicosis**  
 and avian tuberculosis, (case reports) 80 78-84  
 BCG vaccination in, 62 455-474, 69 763-789  
 and bronchogenic carcinoma, (case reports)  
 76 1088-1093  
 of gold miners, lung function in, 77 400-412  
 of other workers, (case reports) 77 839-847  
 pneumoliths in, (case reports) 79 512-517
- silicotuberculosis**  
 resection in, (case reports) 71 137-139  
 therapy, medical and medical surgical, in,  
 78 524-535  
 tuberculosilicosis, surgical therapy in, 77 62-72  
 tuberculosis complicating, chemotherapy in,  
 (correspondence) 79 818  
 welders, respiratory disorders in, (case reports)  
 71 877-884
- Pneumoencephalography** in tuberculous men-  
 ingitis, 74 835-855
- Pneumoliths in silicosis**, (case reports) 79 512-517
- Pneumonectomy**  
 for pulmonary hemorrhage in tuberculosis,  
 (case reports) 61 426-430  
 in pulmonary tuberculosis, 77 73-82, 260-270,  
 78 822-831  
 pregnancy after, 78 563-579  
 spontaneous pneumothorax after, (case reports)  
 62 116-117  
 and streptomycin, in streptomycin-refractory  
 pulmonary tuberculosis, (case re-  
 ports) 66 605-614
- Pneumonia**  
 acute, and bronchiectasis, 76 761-769  
 and bronchogenic carcinoma, in adults, 76 47-63  
 Friedlander's, 61 465-473  
 hypoid, (case reports) 64 572-576  
 tuberculin induced, in lungs of sensitized rab-  
 bits, adrenocorticotrophic hormone in,  
 64 508-515
- tuberculous**  
 due to organisms resistant to streptomycin  
 and isoniazid, (case reports) 70 881-  
 891  
 massive, management of, 64 41-49



*Pneumonia, tuberculous, cont*

- in Negroes, 68 382-392
  - streptomycin therapy in, 60 343-353
- Pneumonitis, Löffler's, during antituberculosis chemotherapy, (case reports) 74 445-453
- Pneumonolysis, intrapleural, closed, 59 240-258
- Pneumoperitoneum
  - air embolism in, 69 396-405, (case reports) 72 537-538
  - appendicitis during, 61 353-354
  - artificial
    - abdominal pneumocele after, (case reports) 60 520-523
    - complications of, 64 645-658
    - effect of ballistocardiograms of patients with chronic disease, 66 52-57
  - compared with pregnancy in young women with functionally normal lungs and serial observations during pregnancy and postpartum pneumoperitoneum, 67 755-778
  - complicated by pneumothorax, (case reports) 63 710-713
    - left sided, (case reports) 72 663-666
    - and peritoneal effusion, (case reports) 66 90-94
    - ruptured diaphragm resulting in spontaneous, (case reports) 63 587-590
  - complicated by scrotal pneumocele, (case reports) 74 622-623
  - electrocardiogram in, 61 335-345
  - diaphragmatic rupture and fatal tension pneumothorax, (case reports) 60 794-800
  - gastrointestinal changes in, 66 750-757
  - hepatolysis in, (case reports) 69 297-299
  - induction, complicated by mediastinal emphysema, (case reports) 63 591-596
  - inflation of esophageal hernial sac during, (case reports) 75 823-827
  - with inguinal hernia, (case reports) 60 524-526
  - intrapertitoneal hemorrhage in
    - caused by splenic rupture after, (case reports) 77 291-294
    - occurring as complication of, 63 116-118
  - mediastinal emphysema after, (case reports) 68 775-781
  - and millwheel murmur presumably caused by air embolism, (case reports) 70 1092-1095
  - in nonsurgical treatment of esophageal hiatal hernia, (case reports) 78 623-631
  - pelvic complications of, (case reports) 62 109-111
  - with phrenic paralysis for pulmonary tuberculosis, 61 323-334
  - physiologic effects on respiratory apparatus, 60 706-714
  - with pregnancy, (case reports) 62 219-222, 66 86-89
  - in pulmonary tuberculosis
    - effect on liver function, 65 539-595
    - respiratory effect of, 70 672-688
  - spirometric studies in, 65 465-476
  - spontaneous pneumothorax after, (case reports) 71 295-298
  - with streptomycin-PAS, in pulmonary tuberculosis, 69 963-967
  - sulfur hexafluoride in, 76 1063-1070
  - ten years of, 63 62-66
  - therapeutic
    - complicated by mediastinal emphysema, (Notes) 76 897-898
    - diaphragmatic pneumocele in, 69 745-758
    - with spontaneous right sided pneumothorax, 63 67-75
    - with torsion of the spleen, (case reports) 62 439-440, 70 166-170, correspondence) 70 923
    - transdiaphragmatic eventration in, (case reports) 69 1045-1050
- Pneumotherapy and chemotherapy, possible antagonism (correspondence) 70 533-534, 71 600-602, 71 766
- Pneumothorax
  - artificial, (correspondence) 72 252, 694
  - angiocardiology in, 62 353-359
  - induction, (correspondence) 69 844-845, (Notes) 71 596-599
  - in lower lobe tuberculosis, 59 50-52
  - in middle aged and elderly patients, 69 968-979
  - statistical analysis of 557 cases initiated in 1930-1939 and followed in 1949
    - I Influence of clinical findings before induction and late results, 64 1-20
    - II Fate of the contralateral lung, 64 21-26
    - III Influence of features of management after induction on early and late results, 64 27-40
    - IV Incidence, mortality, and factors associated with complicating tuberculous empyema, 64 127-140
    - V Incidence, degree, and causative factors of pulmonary contraction or "unexpandable lung," 64 141-150
    - VI Results in various selected series of cases, 64 151-158
  - complication of pneumoperitoneum, (case reports) 63 710-713
  - extrapleural, 67 3-21
    - complicated by extrapleural hematoma, streptokinase-streptodornase in, 63 547-555
  - fluid, functional prophylaxis in, 66 134-150
  - induction, (correspondence) 70 373-374, 755, 72 268-273

*Pneumothorax induction cont*

- lung trauma at, 60 557-563
- traumatic, (correspondence) 70 536-537
- left sided, complicating pneumoperitoneum, (case reports) 72 663-666
- by lung puncture or "orthodox" technique, (editorials) 69 121-124
- machines and needles, historic collection, (correspondence) 80 278
- recurrent, 60 683-698
- spontaneous, 72 257-267
  - bilateral, and spontaneous mediastinal emphysema, (case reports) 61 883-886
  - in histoplasmosis, complicated by pregnancy, (case reports) 75 111-121
  - nontuberculous, 60 683-698
  - after pneumonectomy, (case reports) 62 116-117
  - after pneumoperitoneum, (case reports) 71 295-298
  - in pulmonary tuberculosis, 74 351-357
  - resection, 72 801-809
  - result of ruptured diaphragm complicating pneumoperitoneum, (case reports) 63 587-590
  - right sided, complicating pneumoperitoneum, 63 67-75, (case reports) 66 90-94
- and streptomycin, in pulmonary tuberculosis, 59 539-553
- tension, following diaphragmatic rupture during pneumoperitoneum, (case reports) 60 794-800
- therapeutic,
  - with massive hemothorax, (case reports) 60 654-659
  - in middle aged and elderly patients, 63 325-331
  - present status, 62 (Supplement, July 90-97)
- tuberculous, spontaneous, 59 619-623
- Polycythemia
  - idiopathic hypoventilation, and cor pulmonale, (case reports) 80 575-581
  - with tuberculosis of spleen, (case reports) 60 660-669
- Polyoxyethylene ether *See also* Triton WR 1339
  - action against tubercle bacilli, 69 690-704
  - failure to protect against tuberculin shock in guinea pigs, (Notes) 79 382-383
- Polysaccharide(s)
  - chemical and biological properties, 59 86-101
  - isolation by alcohol fractionation from tuberculin of, 59 86-101
  - serum, during sensitization and development of tuberculosis, 62 67-76
  - skin tests
    - Blastomyces dermatitidis* and *H. capsulatum*, in humans, (Notes) 80 264-266
    - reactions, 77 983-989
    - in tuberculosis, interference with antibodies, 73 547-562
- Polysclerosis, tuberculous, (Notes) 80 259-261
- Polyvinyl-formal sponge prosthesis in pulmonary diseases, 74 581-589
- Potassium para aminosalicylate, clinical use, 71 220-227
- Potassium iodide
  - PAS, in chronic fibroid tuberculosis, 64 77-80
  - streptomycin in experimental tuberculosis in guinea pigs, 64 102-112, 66 680-698
- Pott's disease, 62 (Supplement, July 48-67)
- PPD *See* Tuberculin
- Precipitin
  - agar diffusion techniques, 73 637-649
  - test for carbohydrate antibodies in tuberculosis in humans, (correspondence) 59 710-712
- Prednisone *See* Hormones
- Pregnancy
  - complicating artificial pneumoperitoneum, 62 219-222
  - complicating chronic pulmonary histoplasmosis with spontaneous pneumothorax, (case reports) 75 111-121
  - full-term, after thoracic surgery for tuberculosis, 78 697-711
  - and miliary tuberculosis, 62 209-212
  - in tuberculous salpingitis causing acute hematogenous tuberculosis, (case reports) 68 253-262
  - pneumoperitoneum during, (case reports) 66 86-89
  - pulmonary function in
    - comparison of pneumoperitoneum and pregnancy in young women with functionally normal lungs, and serial observations during pregnancy and postpartum pneumoperitoneum, 67 755-778
    - serial observations
      - in normal women, 67 568-597
      - in patients with pulmonary insufficiency, 67 779-797
    - and sarcoidosis, (case reports) 63 603-607
    - tuberculous meningitis during, (case reports) 76 1079-1087
    - in tuberculous mother, 65 1-23
- Pressure, pulmonary arterial, and tuberculosis frequency, 78 536-546
- Pressure-flow-volume interrelationships in man, 80 (Supplement, July 138-140)
- Prevention in tuberculosis, (editorials) 74 117-120
- Primary tuberculous focus, local reactivation in lung, 78 547-562
- Prisoners, mass screening program of, in Los Angeles County jail, 74 590-596

- Probenecid**  
 effect on blood PAS concentrations, 66 228-232  
 influence on PAS plasma concentrations, 61 862-867
- Promizole®** See *Thiazolsulfone*
- Prophylactic effects of isoniazid in primary tuberculosis**, 76 942-963
- Prophylaxis**  
 isoniazid  
   in nontuberculous disease, (correspondence) 78 485-487  
   in experimental tuberculosis, 77 999-1004  
 of tuberculosis in children, 74 (Supplement, August 75-89)
- Propyl thiouracil, and triiodothyronine, in experimental tuberculosis**, (Notes) 73 434-437
- Protein(s)**  
 antituberculosis, in bovine spleen, 78 93-100  
 in caseous necrosis, 77 106-119  
 fraction  
   of *M. tuberculosis*, isolation and chemistry of, and its ability to sensitize cells, 66 314-334  
 serum, electrophoretic and chemical, in pulmonary tuberculosis, 67 299-321  
 isolation by alcohol fractionation from tuberculin, 59 511-518, 519-538  
 oral hydrolysate, in pulmonary tuberculosis, 59 511-518, 519-538  
 from paratubercle bacilli, reaction of, and OT, 79 731-737  
 in pleural effusions, 76 247-255  
 purified, derivative, comparison with a purified tuberculin, 66 345-350  
 serum  
   changes, in experimental tuberculosis, 77 120-133  
   electrophoretic  
     and isoniazid therapy, 70 334-343  
     and Middlebrook-Dubos titer in BCG-vaccinated tuberculous children, (Notes) 79 522-524  
     in tuberculosis, 68 372-381  
     in tuberculous guinea pigs, 70 344-348  
   therapy, in pulmonary tuberculosis, 59 511-518, 519-538  
   tuberculin and johnin, fractionation of, 68 425-438, 439-443, 444-450
- Proteinosis, alveolar pulmonary**, (case reports) 78 906-915, 80 249-254
- Prothrombin time determinations during PAS therapy**, (Notes) 67 258-260
- Pseudocavities, roentgenographic**, 71 529-543
- Pseudomonas aeruginosa*, self-inoculation with, by a diabetic woman**, (case reports) 69 818-823
- Psittacosis, antibodies in, tetracycline influence on**, 74 566-571
- Psychologic scale for irregular discharge prediction**, 73 338-350
- Psychology in tuberculosis**, 71 201-219
- Psychoses**  
 in tuberculous patients, 59 289-310, 72 107-116  
   collapse therapy in, 67 232-246  
   toxic, from isoniazid, (case reports) 79 799-804
- Psychosocial factors in pulmonary tuberculosis**, 75 768-780
- Psychotics, tuberculosis in**, (editorials), 68 782-785
- Puerto Rico**  
 tuberculosis in, 67 132-153  
   childhood, 76 388-397  
   mortality, since 1950, (Notes) 70 1099-1101
- Pulmonary** With the exception of Pulmonary function, below, see listings under Lungs and specific conditions
- Pulmonary function**  
 air velocity index, 62 17-28  
 airways obstruction, chronic, pulmonary diffusion in, 71 249-259  
 alveolar-arterial oxygen tension gradient in pulmonary disease, 69 71-77  
 alveolar-capillary block from leukemic infiltration of lung, (case reports) 80 895-901  
 alveolar respiratory surface, effective, and other lung properties in normal persons, 70 296-303  
 arterial oxygen lack measured by oxygen tension, 79 315-322  
 Bellows apparatus in studies, 80 724-731  
 bilateral residual volume determination  
   in healthy subjects, 78 368-375  
   in tuberculous subjects, 78 376-390  
 blood flow through nonventilated portions of lung, 68 177-187  
 in bronchitis, physiologic defects in, 78 191-202  
 bronchspirometry  
   after pulmonary decortication, 66 509-521  
   before and after segmental resection and lobectomy for, 75 710-723  
   in thoracic surgery, 75 730-744  
   before and after thoracoplasty, 75 724-729  
   values, significance of, 75 699-709  
   vital capacity in, (Notes) 76 320-321  
 after bullae excision, 77 387-399  
 carbon dioxide narcosis treated by resuscitator, 74 309-316  
 carbon monoxide diffusing capacity during exercise, 74 317-342  
 cardiopulmonary function  
   in Boeck's sarcoid, cortisone in, 67 154-172

*Pulmonary function cardiopulmonary function, cont*

- in bronchiectasis, pre- and postoperative, 69 869-914
- in emphysema *See* emphysema, below
- in hematogenous pulmonary tuberculosis in patients receiving streptomycin, 64 583-601
- in pulmonary fibrosis, 80 700-704
- circulation
  - in emphysema *See* emphysema, below
  - pulmonary capillary, 71 822-829
- coal miners, respiratory gas exchange in, 61 201-225
- corticotropin-cortisone effects on, 64 279-294
- after decortication, 63 231-251
- bronchspirometric study, 66 509-521
- diffusing capacity
  - during exercise, 80 806-824
  - without airway obstruction, 78 173-179
- dyspnea in beryllium workers, 59 364-390
- in emphysema
  - air flow physics in, 80 (Supplement, July 123-125)
  - bullous, bilateral, (case reports) 71 867-876
  - chronic
    - energy cost and control of breathing, 80 (Supplement, July 131)
    - obstructive, cardiopulmonary function in, 80 689-699
    - pressure-volume and pressure-flow relationships, 74 210-219
    - respirators in, 80 510-521
    - routine tests in correlation of compliance and mechanical resistance, 74 220-228
  - circulation dynamics in, during exercise, 80 (Supplement, July 128)
  - in coal miners, ventilatory measurements in, 59 270-288
  - diagnosis of, oximeter test in, 80 705-715
  - diffusing capacity in, 71 249-259
  - intermittent positive pressure breathing in, 76 33-46
  - mechanics of ventilation in, 80 (Supplement, July 118-122)
- functional residual capacity measured with two closed-circuit helium-dilution methods, 74 729-738
- gas mixing in tuberculous lung, 74 343-350
- idiopathic hypoventilation, polycythemia, and cor pulmonale, (case reports) 80 575-581
- impaired function, basal respiratory minute volume as index of, 65 505-510
- intermittent positive pressure breathing
  - in bronchopulmonary disease, 71 693-703
  - in emphysema, severe, pulmonary, 76 33-46
  - in tuberculosis, pulmonary, 72 479-486

- intrapulmonary gas mixing after lung surgery for tuberculosis, 78 1-7
- maximal breathing capacity, predicted, in obese subjects, (Notes) 80 902-903
- mechanics of breathing
  - effects of smoking on, 77 1-16
  - gas exchange, and pulmonary circulation, influence of ventilatory mechanics, 80 53-58
  - physical properties of lung, 80 38-45
  - respiratory work, 80 46-52
- in mitral stenosis, 79 265-272
- oxygen
  - breathing, in respiratory acidosis, 77 737-748
  - diffusing capacity during exercise, 80 806-824
- Parkinson's syndrome, dyspnea as symptom, 78 682-691
- after phrenic crush, 71 676-692
- pneumoperitoneum effects
  - physiologic, 60 706-714
  - in pulmonary tuberculosis, 70 672-688
- in pregnancy, 67 568-597, 755-778, 779-797
- pressure-flow-volume interrelationships in man, 80 (Supplement, July 138-140)
- in pulmonary tuberculosis, 79 474-483
- reflex responses to inflation or deflation of lungs and role in respiratory regulation 73 519-528
- in resection
  - bilateral, 79 468-473
  - partial, functional results after, 76 983-987
  - pulmonary, before and after, 72 453-464
  - segmental, for bronchiectasis, 77 209-220
- residual air measurements by helium and oxygen, 76 601-615
- respiratory disorders in welders, (case reports) 71 877-884
- respiratory infection, importance of, 64 461-467
- in silicosis in gold miners of Witwatersrand, 77 400-412
- spirometers, aneroid and water compared, 61 582-585
- spirometry
  - in maximal breathing capacity, compared with Douglas Bag measurement, (Notes) 79 253-255
  - in pneumoperitoneum, 65 465-476
- tests, 79 457-467
  - direct-writing ear oximeter in, 74 511-532
  - in evaluating patients for thoracoplasty, 63 76-80
  - index of expiratory force, 78 692-696
  - maximal midexpiratory flow, 72 783-800
  - for detecting ventilatory obstruction, 78 180-190

*Pulmonary function tests and*

- Report of the ATS Subcommittee, 62 151-154
- simple, for sanatorium or clinic, 60 119-167
- single breath oxygen, terminal rise in, 75 715-755
- in tuberculosis, 71 313-318
- and other chronic pulmonary diseases, 70 112-151
- ventilation
  - defective, analysis by timed capacity measurements, 64 256-278
  - disturbances determined by helium dilution method, 70 150-156
  - efficiency, nitrogen clearance in, 72 165-178
  - measurement, convenient method based on Venturi principle, 75 303-318
- Purified protein derivative *See* Tuberculin, PPD
- Purpura, thrombocytopenic, and bronchogenic carcinoma, (case reports) 67 509-513
- Pyrazinamide
  - activation, in acidic environments *in vitro*, (Notes) 70 718-751
  - alone and in combination in experimental tuberculosis, 76 613-659
  - antituberculosis activity *in vitro* and in guinea pigs, (Notes) 70 367-369
  - ATS statement on, 75 1012-1015
  - cycloserine, in pulmonary tuberculosis, (Notes) 78 927-931
  - hepatotoxicity, 80 371-387
  - induced liver damage, by serum enzyme determinations, 80 555-565
  - inducing hepatitis, (case reports) 77 855-862
  - isoniazid
    - causing hyperuricemia, (Notes) 71 289-292
    - compared with isoniazid-PAS, 73 704-715
    - in experimental tuberculosis, 69 319-333
    - in low dosage, 71 100-109
    - in patients with previous isoniazid therapy, (Notes) 75 846-848
    - in pulmonary tuberculosis, 69 319-350
    - with isoniazid, (Notes) 70 713-717
  - in tuberculosis, (Notes) 72 851-855
  - lack of significant *in vitro* susceptibility of *M. tuberculosis* to, on solid media, 67 391-395
  - measurement, in blood and kidneys, 75 105-110
  - nicotinamide, intracellular activation of, 74 718-728
  - paired with other drug combinations, 80 627-640
  - resistant tubercle bacilli, 74 572-580
  - susceptibility
    - of isoniazid-resistant tubercle bacilli, (Notes) 72 840-842
    - in vitro*, of tubercle bacilli to, (Notes) 65 635-636

toxicity, 70 121-129

in tuberculosis

experimental

in guinea pigs, 65 519-522

in mice, 65 511-518

pulmonary, 65 523-546, (case reports) 69 143-150, (Notes) 76 1097-1099

alone and in combination with streptomycin, PAS, or isoniazid, 70 113-122

with isoniazid or PAS, (Notes) 70 102-104

-viomycin, in surgical therapy of tuberculosis, 77 83-92

Pyridine derivative in experimental tuberculosis, (correspondence) 60 269-271

Pyridine nucleotides in experimental tuberculosis, before and during isoniazid therapy, 70 153-161

Pyridoxal, neutralization of isoniazid, 76 568-578

Pyridoxine

-isoniazid

concurrently administered, (Notes) 71 471-473

delay of antagonism *in vivo*, (Notes) 76 1100-1105

effect on

antituberculosis activity *in vivo*, (Notes) 71 898-899

metabolism, 75 594-600

massive dose, in pulmonary tuberculosis, 78 174-177

relationship in children, 75 591-600

Pyrogallol-peroxidative activity, relationship to isoniazid resistance in *M. tuberculosis*, (Notes) 75 670-671

## Q

Quaternary ammonium compounds, and penicillin, in sputum cultures, 72 98-106

Quartz *See* Pneumoconiosis

## R

Rabbits *See* Tuberculosis, experimentalRadioactive iodine ( $I^{131}$ ) in chronic pulmonary insufficiency, 80 181-187

Radiation

effects and protection from, in chest roentgenographic surveys, (ATS statement) 80 115-117

hazard

in photofluorography, method to reduce, 77 923-930

in roentgenography, 77 203-209, 375-386

therapy

in middle lobe syndrome in children, (case reports) 76 291-297

*Radiation therapy, chest*

- in lymphadenitis, tuberculous
- cervical, (Notes) 71 641-644
- peripheral, 68 157-165

*Radiography See Roentgenography**Radiology See Roentgenography**Rats*

- in experimental tuberculosis
- albino
- comparison of cortisone treated and alloxan diabetic, 65 603-611
- cortisone-streptomycin in, 65 596-602
- isoniazid in, 65 376-391, 392-401

*Reaction, tuberculin See Tuberculin**Reconstruction, surgical, of the trachea, 62 176-189**Recrudescence in early phthisis, 65 673-691**Rectum, absorption of the sodium salt of PAS from, 63 213-219**Rehabilitation*

- and occupational therapy in tuberculosis hospitals, (correspondence) 79 680, 80 115-117
- from standpoint of tuberculosis physician, 62 (Supplement, July 76-79)
- of the tuberculous, (editorials) 65 481-483, (correspondence) 80 111-112
- in Europe, 66 104-108
- in Philadelphia, 62 190-208

*vocational*

- justification of, in tuberculosis hospital, 80 59-64
- in pulmonary tuberculosis today, (editorials) 78 647, 649
- in tuberculosis, (correspondence) 79 543-545

*Relapse*

- bacteriologic, in pulmonary tuberculosis, after chemotherapy, (Notes) 71 302-304
- in noninfectious tuberculosis, chemotherapy to prevent, (correspondence) 80 108
- rate, in pulmonary tuberculosis, with and without chemotherapy, 79 612-621
- of tuberculous lesions, during and after chemotherapy, 80 (Supplement, October 47-71)

*Renal See Kidneys**Research*

- creative spirit in, (editorials) 64 113-116
- in tuberculosis
- acceleration of, (editorials) 71 140-143
- cooperative clinical, (editorials) 68 263
- cost, (editorials) 60 527-531
- in the United States, 60 393-405

*Resection(s)*

- bilateral
- pulmonary function in, 79 468-473
- in pulmonary tuberculosis, 74 367-376, 75 259-265

- for bullous emphysema, 77 387-399
- coccidioidal cavity, recurrent, after, (case reports) 71 131-136

*for cor pulmonale, 77 387-399**of lesions*

- post-treatment residual, 73 165-190
- pulmonary
- bacteriologic study of, 66 36-43
- clinical and bacteriologic correlation of, 70 689-700
- tubercle bacillus in, 66 44-51

*pulmonary*

- as adjunct in pulmonary tuberculosis, 74 29-41
- bronchial disease in specimens, 68 657-677
- for bronchiectasis, bronchograms before and after, 69 657-672
- drainage after, (Notes) 69 636-637
- for drug-resistant cavitary tuberculosis, using ancillary drugs, 79 780-789
- in middle aged and elderly, 73 40-51
- partial, functional results after, 76 983-987
- pleural tent in, 73 831-852
- in rabbit, (Notes) 73 123-127
- in silicotuberculosis, (case reports) 71 137-139

*streptomycin in, 67 22-28**in tuberculosis, 59 10-29*

- bilateral, 68 885-901
- bronchial ulceration after, 69 84-91
- isoniazid-treated, 70 102-107, 70 285-295
- with simultaneous thoracoplasty, 65 159-167

*in tuberculous bronchitis, 61 185-192**segmental, 69 554-565**bronchspirometry before and after, 75 710-723**and lung function, 72 453-464**specimens, tuberculous disease in, 71 830-840**after thoracoplasty, 60 406-418**thoracoplasty failure as indication for, 62 434-438**in tuberculosis**pulmonary, 71 349-360, 73 79-98**drug resistance in, 75 781-792**in Hawaii, 80 6-11**noninfectious patient with cavity, 74 169-177**Reserpine, in treatment of tuberculous mental patients, (Notes) 74 457-461**Residual air See also Pulmonary function**measurements by helium and oxygen, 76 601-615**Residual volume**bilateral**determination**in healthy subjects, 78 368-375**in pulmonary tuberculosis, 78 376-390*

- Resistance  
     acquired  
         isoniazid in, (Notes) 79 97-101  
     cross, microbial, to drugs, 69 267-279  
     relationship of fluctuation of tuberculin reaction in different geographic areas to, 63 121-139  
     to tuberculosis, concept of, 62 (Supplement, July 3-12)
- Respiration *See also* Pulmonary function  
     alveolar surface, effective, and other pulmonary properties in normal persons, 70 296-303  
     disorders, in welders, (case reports), 71 877-884  
     effect of pneumoperitoneum on, 70 672-688  
     infection, importance of, 61 161-167  
     regulation of inflation reflexes, 73 519-528
- Respirators, in chronic pulmonary emphysema, 80 510-521
- Respiratory function *See also* Pulmonary function  
     and altitude, 79 157-167  
     impaired  
         basal minute volume as index of pulmonary function and, 65 505-510  
         in pulmonary tuberculosis, 71 333-318  
     tests *See* Tests  
     in tuberculosis and other chronic lung diseases (Soviet translation), 79 142-151
- Respiratory gas exchange, in anthracite coal miners with pulmonary complaints, 61 201-225
- Respiratory infection, importance of, 64 461-467
- Respiratory quotients of tubercle bacilli at low oxygen tension, (Notes) 67 669-670
- Respiratory surface, alveolar, in normal persons, 70 296-303
- Respiratory tract, viral infections of, 80 315-325
- Respiratory work, in mechanics of breathing, 80 46-52
- Rest and exercise in minimal pulmonary tuberculosis, 69 50-57
- Resuscitator, positive negative, in carbon dioxide narcosis, 74 309-316
- Reticulo-endothelial system, response to "purified wax" and lipopolysaccharide of tubercle bacilli, 70 793-805
- Rhesus monkey *See* Monkeys
- Rheumatism, lung disease simulating, (case reports) 80 732-737
- Rib(s)  
     contralateral fractures during thoracoplasty, (case reports) 66 233-239  
     supernumerary, 59 76-77  
     from thoracoplasty, as possible source of homogenous bone grafts, 63 210-212
- Riboflavin, as indicator of isoniazid ingestion, (Notes) 80 415-423
- Rimifon® *See* Isoniazid
- Rimino compounds, in experimental tuberculosis, 78 62-73
- Ring method, for studying tubercle bacilli in serum medium, (Notes) 77 521-528
- Ristocetin, in murine leprosy, (Notes) 79 673-676
- Rocky Mountains, pulmonary calcifications in region of, 59 613-619
- Roentgenography  
     admission, routine, at Los Angeles County Hospital, 69 910-956  
     chest  
         interpretation of, 61 225-218  
         survey  
             on private patients, (correspondence) 66 502  
             and X-ray radiation effects and protection, ATS statement, 80 115-117  
     of diffuse pulmonary lesions, (correspondence) 60 536-538  
     duplication  
         of films by artificial solarization, 61 725-729  
         solarized, (Notes) 75 139-141  
     in emphysema  
         diagnosis, 80 705-715  
         microradiography, 80 (Supplement, July 104-112)  
     in histoplasmosis, 76 173-194  
     as index of drug effect in rabbits, 68 65-74  
     magnifying multipurpose viewer for films, 68 788-790
- mass  
     dual reading in, 61 443-464  
     among immigrants to Israel, (Notes) 69 837-840  
     lesions undetected in, 64 249-255  
     in pulmonary tuberculosis, appraisal, 60 466-482  
     screening program in Los Angeles County Jail, 74 590-596  
     in small hospitals, (editorials) 64 313-317  
     subsequent course of persons considered to have tuberculosis, 68 9-23  
     survey, 59 494-510  
         of community, pulmonary nodules found, 79 427-439  
         of prisoners in San Joaquin County, 73 882-891  
         in tuberculosis, 65 451-454  
         in Washington, D C, 1948, 66 548-566  
     radiation hazard, 77 203-208  
     in pulmonary tuberculosis, compared with surgical findings, (Notes) 71 452-456  
     unreliabilities in tuberculosis diagnosis, 69 566-584  
     pseudocavities on, 71 529-543
- Roentgenotherapy *See* X-ray therapy
- Rutin, inhibiting tuberculin reaction, 59 701-706

## S

- Salicylate, action in tubercle bacilli, 69 705-709
- Salizid® *See* Isonicotinyl salicylidene hydrazine
- Salpingitis, tuberculous, in pregnant patient, causing acute hematogenous tuberculosis, (case reports) 68 253-262
- Sanatorium for tuberculosis, pericarditis in, 76 636-642
- San Joaquin County (California), mass survey of prisoners, 73 882-891
- Sarcoidosis, 61 299-322, 62 403-407, (correspondence) 75 852-855
- BCG vaccination in, 62 408-417
- and beryllium poisoning, 74 885-897
- Boeck's sarcoid, 61 730-734, 62 231-285
- cardiopulmonary function in, cortisone in, 67 154-172
- cytolysis test *in vitro*, 63 672-673
- etiology, secondary factors in, (Notes) 71 459-461
- failure to develop, after oral ingestion of pine pollen, (correspondence) 80 760
- geographic distribution, (Notes) 70 899-900
- ineffectiveness of isoniazid-ipromazid in, (Notes) 67 671-673
- lupus erythematosus cells in, (correspondence) 74 811
- in lymph nodes, effect on tubercle bacilli of products of, 61 730-734
- and panarteritis, (case reports) 60 236-248
- with periarteritis, (case reports) 60 236-248
- and pregnancy, (case reports) 63 603-607
- prognosis, 65 78-83
- pulmonary, evolution of, (case reports) 80 71-77
- reproduction of, in guinea pigs, with injected material, (case reports) 60 236-248
- with terminal hypertension, (case reports) 60 236-248
- transition from open pulmonary tuberculosis to, (case reports) 78 769-772
- with uremia, (case reports) 60 236-248
- Sarcoma *See* Tumors
- Scalene node(s)
- biopsy, 68 505-522, 76 1002-1006
- for diagnosis of histoplasmosis, (case reports) 66 497-500
- in patients with pulmonary calcifications, 72 91-97
- Scalene lymphadenopathy, postmortem study, (Notes) 76 503-505
- Schistosomiasis, pulmonary, chronic, 79 119-133
- School(s)
- medical, teaching of tuberculosis in, 63 365-371
- roentgenograms in, 60 501-513
- tuberculosis case-finding in, 80 (Supplement, October 73-93)
- Sclerosis, multiple, isoniazid in, 70 577-592
- Scotland, tuberculosis findings in Edinburgh, 1954-1955, 77 623-643
- Scotochromogens, source of, (correspondence) 80 277-278
- Seed plants, antibacterial substances active against tubercle bacilli in, 62 475-480
- Segments, pulmonary, anatomic distribution of, 60 699-705
- Selective Service, tuberculosis among registrants in, 60 773-787
- Self-inoculation, of *M tuberculosis* and *Ps aeruginosa* by a diabetic woman, (case reports) 69 818-823
- Sensitivity
- to histoplasmin, (correspondence) 61 269
- to tuberculin
- attempt to transfer with granulocytes, 64 516-519
- in Minnesota students, 75 442-460
- Sensitization, lack of, to PPD-S, 62 77-86
- Septicemia, tuberculous, fulminant, 59 311-316
- Serosal surfaces, tuberculosis of, 61 845-861
- Serologic tests *See* Tests
- Serology
- in relationship of modified sheep and human erythrocytes, 79 622-630
- of tuberculosis
- leukocyte lysis related to, 69 1002-1015
- pulmonary, 68 739-745
- Serum *See also* Blood, Serology
- albumin, interference with inhibitory action of Tween® on D-29 mycobacteriophage, (Notes) 80 443-444
- antimycobacterial, antigenicity of, 79 631-640
- concentrations
- of amphotericin-B in man, (Notes) 77 1023-1025
- of glycoprotein, in tuberculous guinea pigs, 68 594-602
- of isoniazid in tuberculous patients
- effect of amines on, (Notes) 76 152-158
- on isoniazid therapy, (Notes) 68 286-289
- with PAS tablets, (Notes) 77 184-188
- detection of antibodies in tuberculous patients, 77 462-472
- enzymes, in pyrazinamide hepatitis, 80 855-865
- lipase, studies on, (Notes) 78 117-120
- methylene blue reduction time, tuberculosis influence on, (Notes) 70 907-909
- microbiologic assay technique
- for isoniazid metabolism, (Notes) 75 995-998
- for measuring low concentrations of isoniazid, (Notes) 75 992-994
- mucoprotein, in patients on hinconstarch therapy, (Notes) 78 131-134
- mycobacteriophage-inhibiting factor in, 80 12-18
- polysaccharide(s) *See* Polysaccharides



*Serum, cont*protein *See* Proteins

tuberculin neutralizing, (case reports) 62 112-115

tuberculostatic substance in, possessing lysozyme-like properties, 64 669-671

tuberculous

antibodies in, 72 315-335

hemagglutinin adsorption in, 67 657-664

and Tween® 80, effect on phage, 77 131-145

Sex, relationship of, to susceptibility of normal and immunized mice to tuberculosis, (Notes) 80 750-752

## Shock

anaphylactic, due to PAS, (case reports) 77 492-495

lethal, allergic, under streptomycin therapy, in experimental tuberculosis, (correspondence) 75 343-348

Sickle cell anemia *See* Anemia

Silicate restorations (fillings), in teeth, effect of PAS on, (Notes) 68 622-624

Silicosis, *See* PneumoconiosesSilicotuberculosis *See* Pneumoconioses

Sinus(es), tuberculous

of chest wall, 66 732-743

isoniazid-PAS in, 68 535-540

Skeletal tuberculosis *See* Tuberculosis

## Skin

reaction

effect on repeated histoplasmin tests, 66 588-593

and polysaccharides, 77 983-989

to products of paratubercle bacilli, 79 731-737

sensitivity to tuberculin, effect of estrogen on, 59 186-197

tests, histoplasmin H-42 for, (Notes) 77 546-550  
tuberculosis, in children, 74 (Supplement, August 160-169)Slide cultures *See* Cultures

## Smoking

and cardiopulmonary disease, 77 10-16

in chronic obstructive pulmonary emphysema, 76 22-52

effects on breathing, 77 1-9

Sodium salicylate, in tuberculous lymphadenitis, (correspondence) 68 940-941

Solarization, artificial, duplication of roentgenograms by, 61 725-729

Solvents, organic, filtration of mycobacteria from, 77 290-300

Sonic vibration in transfer of tuberculin hypersensitivity, 73 246-250

Sound spectrography in chest examination, 72 12-34

South Africa, Witwatersrand, silicosis of gold miner in, 77 400-412

South America, tuberculosis in, (correspondence) 67 676-677

## Spectrophotometry

in determination of PAS in human urine, (Notes) 64 577-578

measurement of growth of tubercle bacilli by, 62 87-90

Spectroscopy, infrared, in tuberculosis, 63 372-380

Spirometer, aneroid, comparison with water spirometer, 61 582-585

## Spirometry

in maximal breathing capacity, compared with Douglas Bag measurement, (Notes) 79 253-255

in pneumoperitoneum, 65 165-476

## Spleen

bovine, antituberculosis agent in, 78 93-100

rupture of, after complicating pneumoperitoneum, (case reports) 71 291-294

torsion of, associated with pneumoperitoneum, 62 439-440, 70 166-170, 923

Spontaneous hemopneumothorax *See* Hemopneumothorax

Spread or exacerbation of pulmonary tuberculous lesions as result of thoracoplasty, 61 648-661

## Sputum

*Allescheria boydii* in, (case reports) 71 126-130*Aspergillus fumigatus* in, significance of, 80 167-180

collection during local anesthesia, (correspondence) 75 854-855

conversion, and metabolism of isoniazid, (correspondence) 77 869-871

## culture

for *M. tuberculosis*

and microscopy, during isoniazid therapy, 70 349-359

obtained during local anesthesia, (Notes) 74 977

trisodium phosphate transport-digestion method for processing specimen, (Notes) 70 363-366

pancreatin and quaternary ammonium compounds in, 72 98-106

eosinophilia, (Notes) 80 915-918

examination, (Notes) 76 671-674, 675-678, 679-682

for acid-fast bacilli, 59 449-460

following bronchoscopy, (Notes) 77 716-718

infectivity of pulmonary tuberculosis in relation to, 69 724-732

isolation of *H. capsulatum* from, 66 578-587

noninfectious, and persistent cavity, home care in, 77 764-777

PAS in, effect on culture of tubercle bacilli, 68 42-47

*Sputum, cont*

- toxicity of digestants for tubercle bacilli, 60 628-633
- tubercle bacilli in, effect of alcohols on, 68 419-424
- tuberculous
  - decontamination of, by penicillin, (Notes) 67 530-534
  - filtration by membrane filter, (Notes) 77 1019-1022
  - viscous, homogenization of, (Notes) 80 914
- Staphylococcal infection, enhancement with extraction methods, (Notes) 77 1026-1029
- Starch gels, zone electrophoresis in, (Notes) 78 932-933
- Steatorrhea, and tuberculosis (probable), with hypogammaglobulinemia, (case reports) 74 773-782
- Stenosis
  - bronchial, 62 (Supplement, July 80-89)
  - mitral, pulmonary function studies in, 79 265-272
- Sterility, female, caused by tuberculosis, (editorials) 70 1096-1098
- Sterilization, ultraviolet, H<sub>i</sub> Intensity, (Notes) 71 457-458
- Steroids *See* Hormones
- STH *See* Hormones, somatotrophic
- Stilbamidine-PAS-streptomycin, in pulmonary tuberculosis and systemic blastomycosis, (case reports) 68 615-621
- Stomach, tuberculosis of, 61 116-130
- Strains, atypical, growth rates of, in biochemical studies, (Notes) 79 94-96
- Streptococcus faecalis* as cause of pyogenic meningitis, 62 441-445
- Streptodornase-streptokinase *See* Streptokinase-streptodornase
- Streptokinase-streptodornase
  - in extrapleural hematoma, complicating extrapleural pneumothorax, 63 547-555
  - in extrapleural suppurative tuberculosis, 71 1-11
  - in tuberculous and bacterial meningitis, 71 12-29
- Streptomycin *See also* Dihydrostreptomycin
  - activity
    - on H37Rv strain of *M. tuberculosis*, 59 461-465
    - singly and in combination with isoniazid, 67 808-827
    - on tubercle bacilli, 62 582-585
  - bactericidal action on extracellular and intracellular tubercle bacilli, 67 322-340
  - cortisone, in experimental tuberculosis in albino rats, 65 596-602
  - dependent strains of *M. tuberculosis*, (correspondence) 59 219-220
  - dependent tubercle bacilli, 64 192-196
  - pathogenicity of, 63 96-99
  - in development of atypical variants of *M. tuberculosis in vitro*, (Notes) 78 921-926
  - dihydrostreptomycin, toxicity of, 60 564-575
  - effect
    - on bacterial resistance to isoniazid, 67 553-567
    - on bronchocavitary junction in relation to healing, 67 173-200
    - on morphology of tuberculous lesion, 61 525-536
    - on pathology of tuberculous meningitis, 61 171-184
    - on tubercle bacilli
      - electron-microscopy study, 70 328-333
      - in vitro*, 71 556-565
      - in vivo* and *in vitro*, on streptomycin-resistant tubercle bacilli, 66 486-496
  - and enzymatic reactions of *M. tuberculosis*, 65 722-734
  - in esophago-cutaneous fistula, 59 687-691
  - in experimental tuberculous meningitis, 70 714-727
  - in guinea pigs with discrete chronic tuberculous lesions, 66 194-212
  - histopathologic changes in lungs after, 61 543-555
  - historical aspects of its development as a chemotherapeutic agent in tuberculosis, 69 859-868
  - historical notes on, 70 9-14
  - inhibition of growth of *M. smegmatis*, 71 743-752
  - intermittent regimens
    - analysis of 97 patients with pulmonary tuberculosis treated with 1 or 2 grams every third day, 63 275-294
    - comparison with daily dosage schedules in the treatment of pulmonary tuberculosis, 63 295-311
    - and PAS in treatment of pulmonary tuberculosis, 63 295-311
- isoniazid
  - action of *M. tuberculosis* within phagocytes, (Notes) 65 775-776
  - compared with isoniazid and streptomycin-PAS in pulmonary tuberculosis, (Notes) 66 632-635, (Notes) 67 108-113, 539-543
  - effect on course of tuberculosis in rabbit eye, 69 1016-1021
  - in experimental tuberculosis
    - in guinea pigs, 68 575-582
    - of mice, antagonism of, (Notes) 68 277-279
  - in fatal meningitis, (case reports) 72 653-658
  - in murine leprosy, (Notes) 72 846-850

*Streptomycin* cont

- PAS, in combinations, therapeutic and toxic effects of, 69 1-12
- in pulmonary tuberculosis, compared with isoniazid and streptomycin-PAS, (Notes) 68 264-269
- resistance, (correspondence) 75 346-347
  - synergism of, *in vitro*, (Notes) 65 777-778
  - in tuberculosis, incidence of bacterial resistance, (Notes) 67 106-107
- neurotoxicity of, 60 39-44
- oxytetracycline, in pulmonary tuberculosis, 66 534-541, 69 58-70
- paired with other drug combinations, 80 627-640
- PAS
  - aplastic anemia following use of, (case reports) 68 455-457
  - compared with isoniazid and streptomycin-isoniazid in pulmonary tuberculosis, (Notes) 66 632-635, (Notes) 67 108-113, 539-543
  - corticotropin, in pulmonary tuberculosis, 66 542-547
  - cultural properties of *M. tuberculosis* in lesions resected from patients treated with, 68 727-733
  - effect on tubercle bacillus *in vitro* and *in vivo*, 59 554-561
  - with pneumoperitoneum, in pulmonary tuberculosis, 69 963-967
  - in tuberculosis
    - experimental
      - of guinea pigs infected intracerebrally, 64 87-101
      - in mice, (correspondence) 60 808-810
      - pulmonary, (Notes) 72 242-244
      - compared with isoniazid and streptomycin-isoniazid, (Notes) 68 264-269
      - stilbamidine, and systemic blastomycosis, (case reports) 68 615-621
    - and pneumonectomy, in pulmonary tuberculosis, streptomycin-refractory, (case reports) 66 605-614
    - and pneumothorax, in pulmonary tuberculosis, 59 539-553
    - and potassium iodide in experimental tuberculosis in guinea pigs, 64 102-112, 66 680-698
    - in pulmonary resection, 67 22-28
    - pyrazinamide, in pulmonary tuberculosis, 70 413-422
    - regimens, evaluation of, in tuberculosis, 60 715-754
    - resistance
      - gradual, in *M. 607*, (Notes) 75 841-842
      - of *M. tuberculosis*, 62 101-108
      - in pretreatment patients, 72 143-150
      - prevention, in sulfathiazole resistant *M. avium*, (Notes) 76 301-307
  - resistant organisms
    - tuberculous infection with, 61 SS1-SS2
    - tuberculous pneumonia due to, (case reports) 70 881-891
  - resistant tubercle bacilli, 59 402-414, 61 719-724
    - without chemotherapy, 70 637-640
    - infection in children, 80 326-339
    - with tuberculosis, 66 63-76
    - effect of streptomycin on, *in vivo* and *in vitro*, 66 486-496
    - inoculation in reinfection tuberculosis, 74 258-276
    - isoniazid in, 66 477-485
    - in necropsy specimens, 63 449-458
    - pulmonary cavitation in development of, 59 391-401
    - in pulmonary tuberculosis, new and untreated, (Notes) 74 293-296
    - transmission of, (correspondence) 62 227
    - in vitro*, 59 438-448
  - singly, in murine leprosy, (Notes) 72 S46-S50
  - and sulfones in experimental tuberculosis of guinea pigs, 64 102-112
  - susceptibility
    - effect of Triton A-20 and pH value on, 62 91-98
    - of *M. tuberculosis*, 61 578-581, 705-718
    - in vitro*, 59 336-352
  - testing
    - slide culture technique, (correspondence) 59 599
    - solid media for, 62 484-490
    - of tubercle bacilli, 61 569-577
  - tenth anniversary, 70 1-8
  - therapy
    - in experimental tuberculosis, lethal allergic shock in, (correspondence) 75 343-344
    - in tuberculous pneumonia in Negro adults, 60 343-353
  - thiasulfone
    - in miliary and meningeal tuberculosis in children, 61 159-170
    - in pulmonary tuberculosis in 19-day-old infant, 61 747-750
  - toxicity, 60 564-575
    - for auditory and vestibular mechanisms, 60 39-44
  - in tuberculosis
    - avian, in chicks, comparison with dihydrostreptomycin, 60 366-376
    - experimental, 59 664-673, 674-678, 60 62-77
    - genitourinary, 61 518-524
    - intestinal, 60 576-588
    - late results, 77 413-417
    - miliary, (case reports) 60 514-519
    - cause of agranulocytosis, 59 317-324
    - minimal, 65 547-571

*Streptomycin cont*

- pulmonary, (Notes) 73 117-122
    - compared with dihydrostreptomycin, 68 229-237, 238-218
    - first clinical trial, (case reports) 71 752-754
    - five-year outcome, 71 193-200
    - follow-up study on, 62 563-571
    - hematogenous, cardiopulmonary function of patients, 64 583-601
    - hypopotassemia and hyponatremia during treatment, 66 357-363
    - once weekly, 69 980-990
    - and other therapy, (editorials) 60 264-268
    - research project, 59 140-167
    - tracheobronchial, 60 32-38
  - in tuberculous empyema, drug concentrations attained with various vehicles, 66 271-284
    - cellugel as vehicle, 66 285-291
  - in tuberculous enterocolitis, 60 576-588, (case reports) 648-653
  - in tuberculous meningitis, 61 247-256, 62 586-593, 67 613-628
  - tuberculous patients 2½ years after, 61 868-874
  - in tuberculous pericarditis, 59 656-663
  - viomycin, isoniazid, and streptomycyclidene isonicotinyl hydrazine in experimental mouse tuberculosis, (Notes) 68 292-294
- Streptomycyclidene isonicotinyl hydrazine**
- streptomycin, viomycin, and isoniazid in experimental mouse tuberculosis, 68 292-294
- sulfate, in pulmonary tuberculosis, 70 701-713
- Streptovaricin**
- alone
    - in humans, (Notes) 75 659-666
    - in tuberculosis
      - experimental, (Notes) 75 659-666
      - pulmonary, (Notes) 80 426-430
  - discovery and biologic activity, 75 576-583
  - in experimental tuberculosis, 77 976-982
  - isolation and properties, 75 584-587
  - isoniazid
    - controlled clinical trial, (Notes) 80 757-759
    - in experimental tuberculosis, (Notes) 75 659-666
    - in humans, (Notes) 75 659-666
    - in pulmonary tuberculosis, (Notes) 80 424-425, 431-433
  - in murine leprosy, (Notes) 79 673-676
  - in vivo* studies in the tuberculous mouse, 75 588-593
- Stress**
- relationship with adrenocortical function and tuberculosis, 69 351-369
  - request for reprints on adaptive hormones and, (correspondence) 67 677-678

**Students**

- medical and nursing, tuberculosis in, 63 332-338
  - tuberculosis in, (Notes) 76 308-314
- Su 1906, activity on chromogenic mycobacteria, 77 694-702
- Su 3068
- activity on chromogenic mycobacteria, 77 694-702
  - antituberculosis activities of, 77 703-711
- Su 3912
- activity on chromogenic mycobacteria, 77 694-702
  - antituberculosis activities of, 77 703-711
- Sulfaguanidine, activity on H37Rv strain of *M tuberculosis*, 59 461-465
- Sulfathiazole**
- activity on H37v strain of *M tuberculosis*, 59 461-465
  - in prevention of streptomycin resistance in *M avium*, (Notes) 76 301-307
- Sulphydryl compounds, effect on growth of tubercle bacilli, 74 42-49
- Sulfone(s)** *See also* individual names of drugs, e.g., Glucosulfone, Sulfoxone
- in experimental tuberculosis, 60 62-77
  - pharmacologic studies, 60 62-77
  - streptomycin in experimental tuberculosis of guinea pigs, 64 102-112
- Sulfoxone, activity on H37Rv strain of *M tuberculosis*, 59 461-465
- Sulfur hexafluoride, in pneumoperitoneum, 76 1063-1070
- Sulphetrone, clinical toxicity of, 62 160-169
- Surface plate counts, in enumeration of viable tubercle bacilli, 64 353-380
- Surgery** *See also* specific surgical procedures
- in bronchiectasis, cardiopulmonary function before and after, 69 869-914
  - of chest
    - electrocardiographic changes after, 59 128-139
    - peptic ulceration after, 74 358-366
  - in emphysema
    - diffuse, obstructive, 80 825-832
    - pulmonary, 73 191-218
  - indications, in pulmonary tuberculosis, 73 191-218
  - pulmonary *See also* specific procedures
    - Horner's syndrome after, 67 94-100
    - in lupus erythematosus, (case reports) 77 338-345
  - in pulmonary tuberculosis, 73 690-703
    - comparison with roentgenographic findings, (Notes) 71 452-456
    - relationship to chemotherapy, bacteriologic status, and pathology, 80 (Supplement, October 95-115)
  - refusal among tuberculosis patients of, 77 311-322

*Surgery, cont*

- reporting of, (correspondence) 79 679-680
- in spontaneous hemopneumothorax, 71 30-48
- of subpleural blebs, 79 577-590
- thoracic *See also* specific procedures
  - electrocardiographic changes after, 64 50-63
  - major, for tuberculosis, full-term delivery following, 78 697-711
- total statistics, in pulmonary tuberculosis, 68 874-884
- transthoracic, removal of lymph node, causing hemoptysis, (case reports) 65 206-209
- Survey (s) *See also* Case finding, Roentgenography
  - cancer detected in, 62 491-500
  - chest, in tuberculosis, 65 451-454
  - fluoroscopic, in China, 72 356-366
  - international, of pulmonary tuberculosis, (Notes) 73 128-133
- mass
  - in case finding, 59 494-510
  - for pulmonary neoplasms, 62 501-511
  - X-ray, what's wrong with, (correspondence) 60 532-535
- roentgenographic
  - lesions undetected in, 64 249-255
  - on private patients, (correspondence) 66 502
  - in schools and industries in San Antonio (Texas), 60 501-513
  - in small hospitals, (editorials) 64 313-317
  - in Washington (D C ), 1948, 66 548-566
- tuberculin patch test among school-age children in Liberia, (Notes) 67 665-668
- Suture, ligation, and partial thoracoplasty in pulmonary tuberculosis, 70 61-70
- S waves, prominent, electrocardiograms with, 62 307-313
- Sweden, BCG vaccination in, (correspondence) 79 678-681
- Symphysis, guided, 66 134-150
- Symposium on emphysema and the "chronic bronchitis" syndrome, Aspen (Colorado), June 13-15, 1958, 80 (Supplement, July 1-213)
- Symptoms, cardiac, in tuberculous patient, 62 (Supplement, July 98-103)

**T**

- Taurine, in experimental tuberculosis, (Notes) 74 638-640
- Teeth, restorations (fillings), effect of PAS on, (Notes) 68 622-624
- Temperature-influenced mycobacteria, in mice and in chick embryo, 73 650-673
- Terramycin® *See* Oxytetracycline
- Test(s)
  - drug-susceptibility, in tuberculosis, (Notes) 77 350-355, (Notes) 78 111-116

## gel

- diffusion, in tuberculosis, 80 886-894
- double-diffusion, in tuberculosis, 80 153-166
- Histoplasma capsulatum* and *Blastomyces dermatitidis* polysaccharide skin, on humans, (Notes) 80 264-266
- intracisternal, of bacillary virulence, 76 426-434
- maximal expiratory flow, for detecting ventilatory obstruction, 78 180-190
- microcolonial, for virulent mycobacteria, (correspondence) 73 600-601
- mouse, for pulmonary tuberculosis, (Notes) 77 1005-1011, 1012-1016
- neotetrazolium inhibition, 77 662-668
- niacin
  - in differentiation of tubercle bacilli, (Notes) 79 810-812
  - in distinguishing mycobacteria, (Notes) 79 663-665
- oxidation-reduction dye, modification of, for determination of virulence of mycobacteria *in vitro*, (Notes) 66 99
- oximeter, in emphysema, diagnosis of, 80 705-715
- pulmonary function *See* Pulmonary function
- of respiratory function, 79 457-467
  - using direct-writing ear oximeter, 74 511-532
- serologic
  - for tuberculosis
    - absorption in, (Notes) 66 762-764
    - new, 64 675-681
- simple paper strip urine, for PAS, (Notes) 80 585-586
- skin, simultaneous, effect on size of tuberculin reactions, 65 201-205
- tuberculin
  - disc-method, 77 778-788
  - patch, among Liberian school-age children, (Notes) 67 665-668
- urine
  - for detection of isoniazid, (Notes) 80 904-908
  - for detection of PAS in ambulatory tuberculous patients, (Notes) 79 672
- of ventilatory capacity
  - index of expiratory force in, 78 692-696
  - maximal midexpiratory flow, 72 783-800
- Testosterone *See* Hormones
- Tetracycline
  - antituberculosis activity, 72 367-372
  - influence on antibodies in ornithosis, 74 566-571
- Therapeutic Trials Committee of the Swedish National Association Against Tuberculosis PAS treatment in pulmonary tuberculosis, comparison between 94 treated and 82 untreated cases, 61 597-612
- Therapy
  - with paired combinations of antituberculosis drugs, 80 627-640

*Therapy, cont*

- of peripheral tuberculous lymphadenitis, 68 157-164
- physical, post-thoracoplasty, 60 189-205
- Thiazolidinone *See* Su 3912
- Thiazoline *See* Su 3068
- Thiazolsulfone
  - factors determining adequate dosage of, 62 618-631
  - in meningeal tuberculosis, in children, 61 159-170
  - streptomycin,
    - in miliary tuberculosis, in children, 61 159-170
    - in pulmonary tuberculosis, in infants, 61 747-750
- Thiocarbanidin
  - antituberculosis activity *in vitro* and in experimental animal, 78 570-575
  - effect on *M. tuberculosis in vitro* and *in vivo*, 77 301-310
  - isoniazid, in pulmonary tuberculosis, (Notes) 80 590-593
- Thiocarbanilide(s) *See also* Su 1906
  - antituberculosis activity of, in mice, 77 301-310
  - in pulmonary tuberculosis, (Notes) 74 468-470
- Thioethyl compounds, antituberculosis activity of, 74 59-67
  - effect of ventilation on, 74 68-71
  - metabolic cleavage of, 74 78-83
- Thioglycollate medium for differentiating mycobacteria, (Notes) 77 356-358
- Thiosemicarbazone(s)
  - amithiozone
    - carbohydrate metabolism associated with, (case reports) 66 373-377
    - causing agranulocytosis, (case reports) 65 339-343
    - resistance and action in mycobacteria, mechanism of, 80 559-568
    - in selected tuberculous pulmonary lesions, 65 692-708
    - susceptibility of tubercle bacilli to, 63 487-489
    - method for determining, 62 638-644
    - tests for, 62 638-644
  - toxicity,
    - in dogs, 64 659-668
    - hepatic, 64 159-169
  - in tuberculosis
    - experimental, in guinea pigs, effect of in combination with dihydrostreptomycin as compared with PAS-dihydrostreptomycin, 63 339-345
    - pulmonary, 64 170-181
  - antituberculosis activity of, 61 1-7, 8-19
  - chemical studies, 61 1-7
  - 4-acetylaminobenzal
    - in experimental tuberculosis in guinea pigs, 62 144-148
    - effect of, in combination with dihydrostreptomycin as compared with PAS-dihydrostreptomycin, 63 339-345
    - human pharmacology, 62 128-143
  - p*-acetylaminobenzaldehyde, susceptibility of tubercle bacilli to, 63 487-489
  - p*-ethylsulfonyl benzaldehyde (Berculon B) in humans, 68 400-410
  - p*-isobutoxybenzaldehyde, failure as anti-tuberculosis drug in man, (Notes) 68 791-793, 794-795, 796-798, 799-802
- Tibione® *See* amithiozone, above
- in tuberculosis,
  - chemotherapy, 61 20-38
  - experimental, in mice, (correspondence) 60 539
  - in humans, 61 145-157
- Thiourea, substituted
  - antituberculosis activity, 70 121-129, 130-138
  - in experimental tuberculosis
    - in guinea pigs, 70 130-138
    - in mice, 70 121-129
- Thoracic surgery *See* Surgery, *also* names of specific procedures
- Thoracoplasty
  - bronchospirrometry before and after, 75 724-729
  - contralateral rib fractures during, (case reports) 66 233-239
  - deformities, prevention of, 66 436-448
  - disappearance of tubercle bacilli in sputum after, 64 307-312
  - effect of penicillin on wound infection after, 61 346-352
  - failure as indication for resection, 62 434-438
  - gelatin foam in, 61 193-200
  - homolateral, effect of paralyzed hemidiaphragm on, 60 183-188
  - late results after, 59 113-127
  - partial, and suture ligation, in pulmonary tuberculosis, 70 61-70
  - patients, postoperative management of, 61 57-59
  - post-thoracoplasty, physical therapy in, 60 189-205
  - primary, for pulmonary tuberculosis, 78 832-838
  - in pulmonary tuberculosis, 59 113-127, 60 273-287
  - in relation to type of lesion, 60 273-287
  - resection after, 60 406-418
    - pre- and post-, in tuberculosis, 79 204-211
    - pulmonary, simultaneously in pulmonary tuberculosis, 65 159-167
  - results
    - according to type of pulmonary tuberculosis, 62 645-653, 69 930-939
    - necessity for accurate evaluation of, (editorials) 60 383
  - ribs as possible source of homogenous bone grafts, 63 210-212

- Taken place of*  
 spread or exacerbation of pulmonary tuberculous lesions as result of, 61 618-631  
 in tuberculous empyema, 65 522-533  
 ventilatory function tests in evaluating patients for, 63 76-80
- Thoracoscopy, 59 210-218
- Thoracotomy, diagnostic, in idiopathic pleural effusion, 71 951-957
- Thorax  
 removal of calcified lymph node, (case reports) 65 206-209  
 surgery of, broncho-pirometry in, 75 730-744  
 vertical tomography of, 62 170-175
- Thrombocytopenic purpura, and bronchogenic carcinoma, (case reports) 67 509-513
- Thromboembolism, incidence and significance of, in pulmonary tuberculosis, 61 826-834
- Thrombosis of cerebral vessels with necrosis of the basal nuclei, 61 217-236
- Thymoma *See* Tumors
- Thyroid  
 function, in patients treated with isoniazid-PAS, 80 815-818  
 isoniazid action against, (Notes) 71 889-891  
 PAS action against, (Notes) 71 889-891  
 in tuberculosis, native resistance to  
 hyperthyroidism in, 79 152-179  
 hypothyroidism, 79 180-203
- Time factor, in studies of outcome of chronic disease, (editorials) 63 608-612
- Tissue(s)  
 acids, fatty, in resistance of tubercle bacilli in rabbits, 69 710-723  
 animal, tuberculostatic agent present in, (Notes) 63 119  
 cultures  
 mammalian cells and mycobacteria in, (correspondence) 75 317-348  
 mycobacteria in, 77 789-801  
 studies on resistance in tuberculosis, 79 221-231  
 tuberculin reaction in glucose in, 78 712-721  
 internal, allergy of, effect of estrogen on, 59 186-197  
 mycobacteria in, retention and differentiation of, 74 608-615  
 tuberculous  
 granulation, distribution of iron in, 61 560-562  
 tubercle bacilli in, (correspondence) 75 519-520
- Tomography  
 and bronchography, in apical bronchiectasis, 74 388-399  
 vertical, of the thorax, 62 170-175
- Tongue, nicotinamide therapy of changes in, 62 360-373
- Tonsils, faucial, primary tuberculosis of, (case reports) 69 612-617
- Torsion, splenic, 62 139-140  
 and peritoneum, 70 166-170, (correspondence) 70 923
- Trachea  
 anomalous bronchus to the right upper lobe, (case reports) 61 656-670  
 fenestration  
 evolution and early results of, 79 773-779  
 in exploration of bronchial tree, 78 815-821  
 in pulmonary disease, 78 815-821  
 papillomatosis of, (case reports) 71 429-436  
 reconstruction  
 plastic, 61 477-488  
 surgical, 62 176-189  
 tuberculosis, 60 601-620
- Tranquilizer(s)  
 effect  
 on activity of ambulatory tuberculous patients, (Notes) 79 531-532  
 on hospitalized tuberculous patients, (Notes) 78 127-130
- Transaminase, glutamic oxalacetic and pyruvic, in pulmonary tuberculosis, (Notes) 79 251-252
- Trauma, of lung, at pneumothorax induction, 60 557-563
- Treatment failures, (correspondence) 79 105
- Tributyrylase and fatty acids in BCG rabbits, 72 340-344
- 3,3',5 Triiodo L-thyronine in tuberculosis and pneumococcosis, survival time of mice with, 79 339-343
- Triiodothyronine and propyl thiouracil in experimental tuberculosis, (Notes) 73 434-437
- Trisodium phosphate transport digestion method for processing sputum and gastric specimens, (Notes) 70 363-366
- Triton A-20  
 antituberculosis activity of, in mice, 65 716-721  
 -1,1-dimethyl 8 isopropyl-bicyclo decapentane  
 therapeutic activity in experimental tuberculosis and leprosy, (Notes) 75 681-687  
 effect on streptomycin susceptibility of resistant strain of *M. tuberculosis*, 62 91-98
- Triton WR 1339 *See also* Polyoxyethylene ether and malachite green in charcoal media for tubercle bacilli, (Notes) 71 894-897  
 in murine leprosy, (correspondence) 76 915-916
- Trudeau *See also* American Trudeau Society Foundation, Edward L., inauguration of, 62 (Supplement, July 104-113)  
 Sanatorium, closing, (editorials) 71 163-164  
 School of Tuberculosis, inauguration of, 62 (Supplement, July 104-119)

- Trypsin, effect on *M. tuberculosis in vitro*, 76 279-285
- Tubercle bacillus(1) *See also Mycobacterium tuberculosis*
- acid fast
- microorganisms other than, in HeLa cells, growth characteristics of, (Notes) 80 744-746
- wild-type, titration of cord formation as measure of pathogenicity, (Notes) 78 799-801
- activity of streptomycin-PAS on, 59 554-561
- air-borne, isolation of, in a tuberculosis hospital, (Notes) 67 878-880
- amithiozone susceptibility, 63 487-489
- antibacterial substances in seed plants active against, 62 475-480
- antibodies against hemagglutination test for, 63 667-671
- artificial cellular immunity against, 69 690-704
- atypical, pulmonary disease from, (case reports) 80 738-743
- autolysis and growth of two strains, 65 75-82
- avian, characteristics and resistance of, 76 435-450
- in bone marrow, 63 346-354
- bovine
- effect of calf lung fatty acids on, 75 630-637
- virulence for rabbit, (Notes) 67 265-266
- catalase activity, (Notes) 73 768-772, 76 1007-1015
- and virulence, 78 735-748
- catalase-positive and -negative, 74 42-49
- centrifugation for concentrating, (Notes) 76 899-901
- charcoal diluent for, 70 989-994
- counting chambers for, (correspondence) 70 376-377
- cultures
- "bluing" phenomenon as contamination source, (Notes) 80 95-99
- direct, in patient's blood, as drug therapy test, (Notes) 80 85-88
- filter paper technique for early detection of microcolonies, (Notes) 70 916-919
- media
- blood, 64 551-556
- charcoal, 70 955-976
- Triton WR 1339 and malachite green in, (Notes) 71 894-897
- comparison of, 63 459-469, 470-475
- in egg, (Notes) 73 139-141
- egg yolk, 70 977-988
- negative, procedure for, (correspondence) 68 470-471
- neotetrazolium chloride in (Notes) 68 625-628
- by test tube or bottle, (correspondence) 77 1030-1031
- cycloserine effect, (Notes) 72 685-686
- cytology, phase contrast studies in, (Notes) 73 294
- detection
- by egg embryo procedure, (Notes) 76 315-319
- of small numbers
- concentrating agents' lethal action on, 69 991-1001
- from dispersed cultures, using mice, guinea pigs, and artificial media, 65 572-588
- differentiation of human from atypical acid-fast, (Notes) 79 810-812
- dihydrostreptomycin resistant, enhancement of, 63 568-578
- dissemination of, in experimental tuberculosis in the guinea pig, 61 399-406
- dissociation of, 62 (Supplement, July 22-33)
- drug resistant, 67 553-567
- detected in sputum by slide cultures, (Notes) 75 331-337
- distribution in lung, 73 406-421
- in pretreatment patients, 72 143-150, 151
- through prolonged chemotherapy, (Notes) 76 871-876
- effect
- of  $I^{131}$ , radioactive, -labeled 3,5-diiodo PAS *in vitro* on, 65 316-324
- on migration of phagocytes *in vitro*, 59 562-566
- of neomycin on, 62 300-306
- of quartz on recoverability, from resected pulmonary lesions, (Notes) 71 308-313
- sarcoid lymph node products on, 61 730-734
- enzymatic digestion and concentration, (Notes) 76 896
- extracellular and intracellular, bactericidal action of isoniazid, streptomycin, and oxytetracycline on, 67 322-340
- extraction
- and fractionation of water soluble components from, 64 602-619
- of proteins and other constituents from, 61 798-808
- gastric washings for, evaluation of four methods for collecting and mailing, 65 617-626
- growth
- affected by sulfhydryl compounds, 74 42-49
- delayed emergence of, (Notes) 75 506-509
- failure of chick embryo extract to accelerate, (Notes) 65 783-785
- inhibited by isoniazid antagonized by ketone compounds, (Notes) 68 273-276
- measurement, 62 87-90
- in monocytes from normal and vaccinated rabbits, 69 495-504, (correspondence) 69 1059-1062
- pattern and virulence of, 65 181-186



*Tubercle bacillus(s), growth cont*

- in rabbits given cortisone, (Notes) 77 529-535
- stimulated by desoxyribonucleic acid, 80 866-870
- in Tween®-albumin medium
- BCG, 68 312-371
- strain H37Rv, 68 321-341
- guinea pig virulence of, (Notes) 73 768-772
- hemagglutination reaction, slide test modification of, for antibodies against, 63 667-671
- human
  - effect of calf lung fatty acids on, 75 630-637
  - mycobacteriophage (D 29) inhibited in, by serum factor, 80 12-18
  - virulence
    - for guinea pigs, 73 266-275
    - for rabbit, (Notes) 67 265-266
- inhalation of, protection against, 59 1-9
- inhibition
  - tested in synthetic organic bases, (Notes) 65 631-634
  - by urine, role of ascorbic acid, 69 406-418
- intracellular
  - acidity of, 71 552-565
  - growth and virulence of, 69 479-494
  - isoniazid action on, 66 125-133
- isolation
  - drug-susceptibility, and catalase-testing, from patients treated with isoniazid, 70 852-872
  - from feces and gastric contents of intravenously infected mice, 62 481-483
  - methods, 61 563
  - by microculture method, (Notes) 75 1007-1008
  - from patients treated with streptomycin, 61 705-718
- isoniazid effect
  - on growing and resting, (Notes) 69 125-127
  - lipid, 72 713-717
  - proposed mechanism for, (correspondence) 69 1062-1063
- isoniazid-resistant, 70 91-101, 73 390-405
  - altered growth characteristics of, (Notes) 66 626-628
  - and catalase activity, (Notes) 69 471-472
  - growth requirements, (correspondence) 75 155-156
  - catalase and pathogenicity, 70 641-664
- metabolism, 71 785-798
- pathogenicity
  - in children, 74 (Supplement, August 75-89)
  - human, 71 390-405
- pathology of lesions caused by, (Notes) 74 633-637
- strains infecting children, 80 326-339
- superinfection with, (case reports) 77 168-171

- susceptibility to pyrazinamide, (Notes) 72 840-842
- virulence, 68 548-556, 70 728-733, (correspondence) 70 375-376
  - in guinea pigs and mice, (Notes) 69 464-468
- isoniazid-streptomycin action *in vitro*, 71 556-565
- isoniazid susceptibility, (Notes) 73 768-772
- kojic acid as inhibitor of, 61 738-741
- lipids, 66 28-35
- lipopolysaccharide, reticuloendothelial system response to, 70 793-805
- liquefaction of, mechanism, 63 694-705
- in lungs of rabbits, endocellular proteinases in, 63 694-705
- lysozyme effects, 67 217-231
- metabolism
  - isotopic carbon studies, 71 609-615
  - production of a pharmacologically active metabolite, 63 100-107
  - oxidative, benzoate and salicylate effect, 69 705-709
- methanol extracts, (correspondence) 74 807-808
- immunizing effects on mice, (Notes) 73 781-784
- method
  - for determining susceptibility
    - to amithiozone, 62 638-644
    - to streptomycin, 61 569-577
  - of differentiating from other bacteria, 75 529-537
- in mice, relation between size of infecting dose and survival time, 64 534-540
- microculture method for isolation, (correspondence) 76 159-160
- in mouth wash, membrane filter culture for, 71 371-381
- mutants, isoniazid-resistant, 70 465-475
- in necrotic lesions, biology of, (Notes) 66 629-631
- negative cultures for, procedure with, (correspondence) 69 128
- nonpathogenic, viable, in mice, 75 280-294
- nuclei and mitochondria in, 67 59-73
- P<sup>32</sup>-labeled, virulence of, 79 738-745
- PAS-resistant, 75 608-617
  - genetic considerations of mechanisms involved in, (Notes) 79 371-373
- pathogenicity, and isoniazid susceptibility, 68 734-738
- in pathologic specimens, microculture in blood, (correspondence) 73 785-786
- phase contrast and electronmicroscopic studies on effect of PAS, isoniazid, and viomycin on, (Notes) 73 296-300
- in primary tuberculosis, late discharge of, 79 31
- propagability of, extended incubation on, 77 802-814

*Tubercle bacillus(s), propagability of, cont*

protein, 71 704-721

in pulmonary lesions

isoniazid effect on growth of, (Notes) 70 518-521

resected, 66 41-51, 71 376-387

"purified waw," reticulo endothelial system response to, 70 793-805

resistance

to benzalkonium chloride, 70 312-319

to chemotherapeutic agents, 61 483

to isoniazid, catalase activity, and guinea pig virulence correlated, (Notes) 72 216-251

to pyrazinamide *in vivo*, 74 572-580

of rabbits, relationship of tissue fatty acids to, 69 710-723

to streptomycin in early tuberculosis of guinea pig, 59 674-678

respiratory quotients, at low oxygen tension, (Notes) 67 669-670

ring method, for study of, (Notes) 77 524-528

and saprophytic mycobacteria, differentiation of, (Notes) 74 958-960

self-injection, (case reports) 60 514-519

slide culture method for detection, 60 51-61

in sputum

disappearance of, following thoracoplasty, 64 307-312

effect of alcohols on, 68 419-424

isolation of, in medium, (Notes) 76 703-705

undigested, penicillin as decontaminant in cultures for, (Notes) 67 530-534

staphylococcal infection-enhancing properties of, methods of extraction effects on, (Notes) 77 1026-1029

streptomycin action on, 62 582-585

streptomycin-dependent, 64 192-196

pathogenicity of, 63 96-99

streptomycin-resistant, 59 391-401, 402-414, 438-448, 61 719-724, (correspondence) 62 227, 345-352

without chemotherapy, 70 637-640

in children with tuberculosis, 66 63-76, 80 326-339

effect of streptomycin on, *in vivo* and *in vitro*, 66 486-496

inoculation in reinfection tuberculosis, 74 258-276

in necropsy specimens, 63 449-458

streptomycin-treated, electronmicroscopy of, 70 328-333

survival, in tuberculous lesions, (Notes) 65 637-640, (correspondence) 66 381-382

susceptibility

to antimicrobials, 76 1031-1048

to streptomycin in early tuberculosis of guinea pigs, 59 664-673

*in vitro*

to pyrazinimide, (Notes) 65 635-636

to streptomycin, 59 336-352

suspensions

dilute, standardization of, 59 325-335

influence of dispersion on virulence, 75 488-494

viability for, test of, (Notes) 66 95-98

toxic lipid component

isolated from petroleum ether extracts of young bacterial cultures, 67 629-643

occurrence

in chloroform extracts of young and older bacterial cultures, 67 828-852

in various bacterial extracts, 67 853-858

toxicity of sputum digestants for, 60 628-638

triton malachite green charcoal agar for detection of, (Notes) 75 338-339

in tuberculous tissue, viable and stainable counts on, (correspondence) 75 519-520

viomycin effect against resistance to certain drugs, 63 36-43

viability

with and without chemotherapy, (Notes) 67 874-877

in embalmed human lung tissues, 59 429-437

enumeration of, 74 84-91

by surface plate counts, 64 353-380

in organs of mice, 76 616-635

quartz dust for challenging, (Notes) 69 841-842

virulent

biochemical analysis, 80 535-542

detection of, when coexisting with attenuated bacilli in the mouse, 70 1053-1063

human

in mice, in assessment of chemotherapeutic activity, 64 541-550

toxic effects of DL-serine on, (correspondence) 60 385

influence of "cord factor" in, 77 482-491

influence of cord formation in, 78 83-92

penicillin effect on growth, 80 849-854

in relation to oxidation, 64 520-533

*in vitro* susceptibility in meningeal and military tuberculosis, 74 (Supplement, August 232-240)*in vivo* multiplication, 75 756-767*in vivo* and *in vitro*, biologic differences in, 75 495-500

washed, formation of tuberculin by, in citrate solution, (Notes) 67 526-529

in wax

immunogenicity, 80 216-222

for mouse tuberculosis, 76 752-760

## Tuberculin

## allergy

after BCG vaccination, 70 1064-1082

in guinea pigs vaccinated with BCG, 60 547-556

antigens, with gel diffusion technique, 75 601-607

assay in guinea pigs, 59 692-700

autolytic, transcutaneous tests in children, 60 45-50

compared in BCG-vaccinated and unvaccinated persons, 70 71-90

conversion rates in Kansas City as indication of prevalence of infection, 69 227-233

desensitization, in tuberculous lymphadenitis, (case reports) 60 249-257

dilutions, instability of, (Notes) 72 126-128, (Notes) 74 297-303

dose for single test tuberculin testing, 60 483-486

effect  
on tissues from tuberculin-sensitized hosts, (Notes) 73 581-585

on *in vitro* cytolysis of leukocytes, 60 212-222  
formation of, by washed tubercle bacilli in citrate solution, (Notes) 67 526-529

fractionation, 68 425-438, 439-443

fractions, 59 86-101

effect, on leukocytes from normal and tuberculous animals, 65 250-271

purified, from unheated cultures in testing BCG-vaccinated subjects, (Notes) 69 300-303

for testing BCG subjects, 66 335-344

hemagglutination procedure in study of, 65 272-277

## hypersensitivity

cutaneous, elicited by tuberculin-treated erythrocytes, (Notes) 64 332

in man, tissue culture analysis, 72 577-600

in pulmonary tuberculosis, (Notes) 74 474

transfer, 73 246-250

induced pneumonia in rabbits, adrenocorticotrophic hormone in, 64 508-515

inhibition, by antihistaminic drugs and rutin, 59 701-706

intracutaneous reaction to, topical hydrocortisone acetate ointment at site, (Notes) 79 666-668

intra-dermal, reaction on guinea pig, 69 806-817

intravenous injections, effect on subsequent tuberculin skin reactions in hypersensitive rabbits, 61 556-559

## isolation

of polysaccharides from, 59 86-101

of proteins from, by alcohol fractionation, 59 86-101

## leukocytic sensitivity to

chemotherapy effect on, 77 815-822

in guinea pigs, (Notes) 76 888-891

-negative tuberculosis, 63 501-525, (correspondence) 64 468-469, 469-471

## OT (Old Tuberculin)

and paratubercle bacilli products, skin reaction, 79 731-737

-sensitized sheep and trypsinized human erythrocytes, serologic relation, 79 622-630

patch, survey among school-age children in Liberia, (Notes) 67 665-668

## PPD, 71 704-721

cattle erythrocyte sensitization with, (Notes) 77 177-180

compared with new purified protein, 66 345-350

delayed skin reactivity to, 80 393-403

and other antigens prepared from atypical acid-fast bacilli and *Nocardia asteroides*, 79 284-295

prepared by ammonium sulfate precipitation, (correspondence) 74 810-811

sensitization with, johnin and tuberculin, (Notes) 77 177-180

treatment of tuberculous meningitis in children, 76 832-851

## protein, purified, new

comparison with PPD, 66 345-350

standardization and stability of, (editorials) 80 255-256

## reaction

affected by isoniazid, 74 7-14

analysis, 71 49-73

and antihistaminics, (editorials) 62 555

in children, antihistamine medication on, 60 354-358

cytology, in skin windows in man, 69 216-226  
cytotoxicity of, for sensitized cells, failure to demonstrate *in vitro*, 63 674-678

## effect

of antihistamines on, (correspondence) 60 811, 61 442, 735-737

of simultaneous skin tests, 65 201-205

fluctuation in different geographic areas and its relationship to resistance, 63 121-139

hyperergic reactivity, nonspecific, at site, 69 205-211

and isoniazid treatment, 69 733-744

specificity, (editorials) 63 355-359

stability of, 78 862-870

in tissue culture, glucose in, 78 712-724

in tuberculous patients, 80 569-574

in vaccine assay, 66 351-356

## reactor

resistance, (correspondence) 69 846-847

treatment, (correspondence) 69 843-844

## sensitivity

and adrenocortical function in humans, 73 795-804

*Tuberculin, reaction to*

- in aged, 75 161-168
- attempt to transfer with granulocytes, 61 516-519
- cellular basis in, 68 746-759
- changes in anergic and partially anergic patients treated with antimicrobial therapy, 67 286-291
- and chemotherapy, in rabbits, 79 329-338
- leukocytic transfer of, 78 316-352
- in Minnesota students, 75 142-160
- non-specific, 68 678-694
- passive transfer of, 80 398-403
- with pulmonary calcifications, 59 643-649
- in relation to BCG in Hong Kong, 76 215-224
- in relation to tuberculosis morbidity, 76 517-539
- of skin of forearm and shoulder, (Notes) 72 245
- sensitized
  - cells, inhibition of, *in vitro*, 80 410-414
  - guinea pigs, inhibition of leukocyte migration from, 80 19-25
- shock
  - failure of polyoxyethylene ether to protect against in guinea pigs, (Notes) 79 382-383
  - in tuberculous mice, (Notes) 68 629-630
- skin reaction
  - acceleration, 61 556-559
  - for assay of tuberculin in guinea pigs, 59 692-700
  - correlation with pulmonary lesions in BCG-vaccinated and control persons, 68 713-726
  - effect of antihistaminics on, 62 525-531
  - hydrocortisone acetate ointment in, (Notes) 80 587-589
  - pulmonary tuberculosis in, 78 399-402
- skin sensitivity
  - to BCG, duration variation, 60 541-546
  - effect of estrogen on, 59 186-197
  - in old age, 77 323-328
- standardization
  - in humans, 66 292-313
  - lack of sensitization to PPD-S, 62 77-86
- test
  - in case finding in a general hospital, pilot study, (Notes) 79 378-381
  - in differential diagnosis of pulmonary lesions, 63 140-149
  - disc method, 77 778-788
  - influenced by BCG vaccination, 72 35-52
  - isoniazid effect, (Notes) 67 535-537
- testing
  - in Honolulu schools, 78 871-883
  - of midshipmen and recruits of the Navy and Marine Corps, 62 518-524
  - in New York City, (Notes) 69 1057-1058

- suitable dose for single test, 60 183-186
- in tuberculosis case finding, 78 667-681
- in tuberculous meningitis, (case reports) 74 277-283

**Tuberculoma**

- of the brain, 62 654-666
- of the cerebellopontine angle simulating acoustic neuroma, (case reports) 63 227-229
- and cystic thymoma, possible confusion between, (case reports) 70 155-160
- of lung, 78 103-110
  - simulating bronchogenic carcinoma, 61 431-435
- of mediastinum, 61 327-352

**Tuberculo-protein**, in tuberculosis, interference with antibodies, 73 547-562**Tuberculosilicosis** *See* Pneumoconioses**Tuberculosis**

- and abortion, 70 49-60
- abortive, in guinea pigs, induced by pathologic material containing young tubercle bacilli, (correspondence) 68 467-471
- activation during prednisone therapy, (case reports) 76 140-143
- active
  - ambulatory, outside institutions, (correspondence) 76 506-507
  - chemotherapy for, (correspondence) 63 490-492
  - cycloserine-isoniazid in ambulatory treatment, (Notes) 80 89-94
  - in women, food intake of, 60 455-465
- air hygiene in, study in pilot ward, 75 420-431
- alcoholics with, before and during hospitalization, (editorial) 79 659-662
- ambulatory patients with
  - observations on "open negative" syndrome in, 78 725-734
  - urine test for detection of PAS in, (Notes) 79 672

## in American Negroes, 60 332-342

- in anergic and partially anergic patients treated with antimicrobial therapy, changes in tuberculin sensitivity of, 67 286-291

## prolongation of life, 67 292-298

## in animals, 77 908-922

- with anorexia, insulin treatment for, 60 25-31
- in anthracosis, 65 24-47
- of appendix, 64 182-191

## arcana of

## Parts I and II, 78 151-172

## Part III, 78 426-453

## Part IV, 78 583-603

- arrested, in women, food intake of, 60 455-465
- ascorbic acid in, 64 381-393
- association, effect of isoniazid on program of, (editorials) 66 615-618

*Tuberculosis, cont*

streptomycin in treatment of, 61 875-880

## avian

in chicks, streptomycin and dihydrostreptomycin in, 60 366-376

and silicosis, (case reports) 80 78-81

bacteriologic media, eliminating of precleaning cage-laid hens' eggs in preparation of egg fluid for, (Notes) 79 677

bacteriologic specimens, agitator for, (Notes) 70 176-177

bacteriology, benzalkonium chloride in, (Notes) 80 912-913

## BCG-produced

fatal, 70 402-412, (correspondence) 71 321-323

biologic aspects, 68 1-8

biopsy, needle, of parietal pleura, 78 17-20 of breast, 72 810-824

bronchial, 60 604-620, 63 381-398

major, streptomycin in, 60 32-38

"quiescent," 73 451-471

and bronchiectasis, relationship between, 61 387-398

## bronchogenic

in dog, 73 748-763

role of lymphatics in development of, 67 440-452

*Candida albicans* in sputum of patients with, (Notes) 77 543-545

care, in countries of limited means, (correspondence) 73 444-445

case finding *See* Case finding, Surveys

caseous-pneumonic, isoniazid in, 65 402-428

cavitary drug-resistant, pulmonary resection of, using ancillary drugs, 79 780-789

of lower lobe, 63 625-643

surgery in, 77 593-604

center for, length of stay in, (Notes) 74 961-963

challenge today of, 78 661-666

## changes

in content of serum polysaccharide during sensitization and development, 62 67-76

as seen by a pathologist (ATS conference paper), 79 684-686

chemoprophylaxis, 80 (Supplement, October 1-21)

immunity and prevention in, (editorials) 74 117-120

chemotherapy, 59 223-239, 61 407-421, 67 680-697, 78 251-258, 79 492-496

with amithiozone, 61 20-38

clinical and histopathologic study, 69 247-260 complicating pneumoconiosis, (correspondence) 79 818

in infants and children, 74 (Supplement, August 225-231)

isoniazid, streptomycin, and PAS in combinations, 32-week observations on, (Notes) 70 521-526

long-term, and prognosis in, (correspondence) 70 178

of unhospitalized patients, 70 1042-1052

in childhood, 74 (Supplement, August 1-6), 76 579-587

electrophoretic patterns and hemagglutination reaction, (Notes) 73 964-965

fatal, morphology of, 74 (Supplement, August 7-12)

fever and roentgenographic exacerbations following isoniazid, (case reports) 72 527-536

primary, antimicrobial treatment, (correspondence) 72 398-402

prognosis, 72 513-526

in Puerto Rico, 76 388-397

serum gamma globulin in, 74 15-28

## chronic

experimental, 73 378-389

testosterone in, 70 1020-1029

clinical, neomycin in, 63 427-433

and coccidioidomycosis, 61 887-891

disseminated, 59 415-428

pulmonary, 70 109-120

## contacts

in Edinburgh (1954-1955), 77 623-643

tuberculin sensitivity in, 68 678-694

contamination of eating utensils, (Notes) 74 462-463

## control

among American Negroes, 60 332-342

in hospital personnel, 67 74-84

medical progress in, 70 383-390

program, for student nurses, 73 868-881

and treatment, detention ward in, 74 410-416

in underdeveloped areas, social sciences in, (correspondence) 75 345-346

## corneal

cortisone in, 74 1-6

phase contrast microscopy of, 74 1-6

corticotropin and corticosteroids as adjuvants in, 76 708-710

cortisone and corticotropin in, with and without antimicrobial therapy, 70 623-636

cost, 1956 fiscal estimate, (Notes) 77 172-176

## cutaneous

in children, 74 (Supplement, August 160-169)

inoculation causing, 63 526-537

cyanacetic acid hydrazide in, 74 417-427

cycloserine and isoniazid in, 75 553-575

deaths *See* Tuberculosis, mortality

*Tuberculosis, cont*

- in diabetics, 65 (Supplement, January 1-50),  
76 1016-1030, 77 990-998
- surgery for, 74 747-756
- diagnosis, bacteriologic, 59 589-598, (correspondence) 76 1110-1111
- DIAGNOSTIC STANDARDS of (NTA, 1950), (correspondence) 74 158-159
- discharges
  - irregular, 71 419-428
  - from a hospital, 68 393-399
- drug-arrested, reinfection in guinea pigs with,  
80 554-558
- drug-susceptibility tests in, (Notes) 77 350-355
- effects of amines on serum concentrations of  
isoniazid in patients with, 76 152-158
- elimination of, as public health problem, (ATS)  
79 690-694
- emotional problems in treatment of, (editorials)  
71 299-301
- endobronchial
  - in children, 74 (Supplement, August 246-255),  
77 39-61
  - occult, in surgical lung specimens, 77 931-939
- epidemic, 75 432-441
  - after antityphoid vaccine inoculation, 71  
465-472
- epidemiology, 67 123-131, 75 975-86
  - aspects, 68 1-8
- eradication, (editorials) 59 707-709
- evaluation of method of quantitative air-borne  
infection and its use in study of patho-  
genesis of, 61 765-797
- evolution, in long-observed group, 75 885-896
- experimental
  - 4-acetylaminobenzal thiosemicarbazone in  
and dihydrostreptomycin, compared with  
PAS dihydrostreptomycin, 63 339-345
  - in guinea pigs, 62 144
  - adrenocortical hormones in, (Notes) 77 536-  
538
  - allergy in, 72 171-195
    - gross lesions, and culturable bacilli in mice,  
78 226-234
  - alteration of pulmonary arterial circulation  
in monkeys, 65 48-63
  - antagonism of isoniazid-streptomycin in  
mice infected with *M. tuberculosis*  
H37Rv, (Notes) 68 277-279
  - antituberculosis drug therapy in mice, 69  
104-110
  - arrested, isoniazid in, (Notes) 79 246-250
  - and BCG
    - effect on mice, 68 451-454
    - in guinea pigs
      - cortisone in, 69 511-519
      - vaccine and hyaluronidase in, 68 188-198
    - bovine
      - corticotropin and dihydrostreptomycin  
alone and combined, in rabbits, 67  
201-211
      - strains, 68 220-228
  - chemotherapy
    - effect on leukocytic sensitivity to tuber-  
culin, 77 815-822
    - with sulfones in the mouse, 63 556-578
  - in chicks, avian tuberculosis in, 60 366-376
  - choice of mouse strain, 60 109-120
  - choice and standardization of culture, 60  
90-108
  - chronic, 73 378-389
    - streptomycin in, 66 194-212
  - corticotropin-cortisone in, 68 31-41
    - in guinea pigs, 64 295-306
  - corticotropin and dihydrostreptomycin alone  
and combined, in rabbits, 67 201-211
  - cortisone in, 62 337-344, 65 64-74
    - corticotropin in, with and without anti-  
microbial therapy, 70 623-636
    - dihydrostreptomycin, in guinea pigs,  
(Notes) 67 101-102
    - effect on tuberculous lesions in guinea pigs,  
62 337
    - streptomycin, in albino rats, 65 596-602
    - treated, and alloxan-diabetic albino rats  
compared, 65 603-611
  - cycloserine in, (Notes) 72 117-118, 856-858,  
75 510-513
  - dihydrostreptomycin-PAS in, 62 149-155
  - dissemination of tubercle bacilli in guinea  
pigs, 61 399-406
  - drug screening, in guinea pigs, 68 48-64
  - effects
    - estrogen and chorionic gonadotropin in  
tuberculosis in rabbits, 59 168-185
    - estrogen and gonadotropin on progress of  
tuberculosis, 59 198-218
    - estrogen on tuberculin skin sensitivity and  
allergy of internal tissues, 59 186-197
    - tuberculin fractions on leukocytes from  
normal and tuberculous animals,  
65 250-271
  - embolic, pulmonary, in mice, 69 419-442
  - gauze masks, efficiency in protection of rab-  
bits, 59 1-9
  - genetic resistance in rabbits, 72 297-329
  - glycoprotein serum concentrations in guinea  
pigs, 68 594-604
  - guinea pig omentum as index of chemother-  
apy, 68 583-593
  - guinea pig resistance to tubercle bacilli with  
BCG, (Notes) 72 539-542
  - in guinea pigs vaccinated with BCG, 60 547-  
556
  - 5 heptyl-2-thiohydantoin, 78 74-82

## Tubercle bacillus experimental work

- heterocyclic acid hydrazides and derivatives
  - in, 67 366-375
- hog gastric mucin in, (Notes) 77 1005-1011
- hormone effect on virulent, attenuated, and virulent mycobacteria in mice, 69 700-706
- hyaluronidase in, 63 108-115
- immunity in, 78 203-225
  - natural energy, artificial desensitization in, 78 235-250
- immunogenicity of BCG cultured in bile for guinea pigs, 59 102-105
- infection
  - air-borne, in rabbits, 73 315-329
  - in mice, 60 90-108, 109-120, 121-130, 72 330-339
- inhibited by isoniazid, 75 295-302
- irradiated antituberculosis vaccine and BCG
  - in guinea pigs, 67 311-333
- isolation of tubercle bacilli from feces and gastric contents of mice, 62 181
- isoniazid in, 73 1-18
  - in cats, 65 376-391
  - in combined chemotherapy of mice, 68 411-418
  - derivatives in, 67 354-365
  - in dogs, 65 376-391, 392-401
  - in guinea pigs, 65 365-375, 376-391, 68 75-81
  - early treatment with, 76 732-751
  - in mice, 65 357-364, 376-391, 392-401
  - in prevention, 71 917-939
  - prophylaxis in, (Notes) 77 999-1004
  - in rabbits, 65 365-375, 376-391
  - radioactive, action on, 67 490-496
  - in rats, 65 376-391, 392-401
  - streptomycin, in guinea pigs, 68 575-582
  - PAS resistant, in guinea pigs, 66 477-485
- laboratory operation and design for, 68 212-219
- lethal allergic shock in, (correspondence) 75 343-348
- leukocyte lysis related to tuberculous serology in rabbits, 69 1002-1015
- liquefaction of tubercles, endocellular proteinases in tubercles developing in rabbit lungs, 63 694-705
- meningitis produced by lumbar intrathecal inoculation in guinea pigs, 66 722-731
- in mice
  - antituberculosis chemotherapeutic activity in, 64 541-550
  - lung density as measure of, 77 681-693
  - relation between size of infecting dose and survival time, 64 534-540
  - thiosemicarbazones in, (correspondence) 60 539
  - Triton A 20 alone and in combination with dihydrostreptomycin, 65 718-721
  - in monkeys, 72 204-209
  - isoniazid potentialities in, 71 (Supplement, August 138-153)
  - mycobactin in, 71 566-572
  - neomycin in, 62 345-352
    - in guinea pigs, 62 309-305, 345-352
  - nutrition and immunity in, 77 93-105
  - omentum vs pancreas in, (correspondence) 80 115-119
  - oxytetracycline in, 63 131-140
  - pancreas in, (Notes) 78 791-798
  - PAS, 78 753-759
    - streptomycin therapy in, 62 155-159
  - phagocytic stimulation of, in guinea pigs, (Notes) 73 142-143
  - phenazines in, 78 62-73
  - potassium iodide and streptomycin in guinea pigs, 64 102-112, 66 680-698
  - production of nontuberculous cavities in, by egg albumin, 75 99-101
  - pulmonary resection in rabbit, (Notes) 73 123-127
  - pyrazinamide
    - alone or in combination, 76 643-659
    - in guinea pigs, 65 519-522
    - isoniazid in, 69 319-333
    - in mice, 65 511-518
    - in vitro and in guinea pigs, (Notes) 70 367-369
  - pyridine derivative in, (correspondence) 60 269-271
  - pyridine nucleotides in, before and during isoniazid therapy, 70 453-464
  - quartz dust inhalation effect on BCG, H37Ra, and *M. marinum* strains, 69 766-789
  - in the rabbit, 64 508-515
  - eye
    - adrenal hormones in, 66 175-187
    - as tissue to study, 64 197-206, 207-217
  - roentgenography as index of drug effect in, 68 65-74
  - tissue lipids in, 75 83-92
  - virulence of human and bovine tubercle bacilli in, 67 265-266
  - reproduction of sarcoidosis in guinea pigs, 60 236-248
  - screening of drugs in mice, 69 280-286
  - serum protein in
    - changes in, 77 120-133
    - in guinea pigs, 70 344-348
  - sex differences in mice related to immunity, 75 618-623
  - short-term therapy in, (Notes) 77 867-868
  - skin tuberculin reaction, 59 692-700
  - standardized test, for antituberculosis activity of compounds in, 60 121-130

*Tuberculosis, experimental, cont*

streptomycin in, 59 664-673, 674-678, 60 62-77  
 and PAS  
   in intracerebral infection of guinea pigs, 64 87-101  
   in mice, (correspondence) 60 808-810, 62 156  
   -riomycin, isoniazid, and streptomycylidene isonicotinyl hydrazine in mice, (Notes) 68 292-294  
 streptovaricin in, 77 976-982  
 sulfones in, 60 62-77  
   and streptomycin, in guinea pigs, 64 102-112  
 taurine in, (Notes) 74 638-640  
 test, with guinea pig, for tuberculostatic agents, 60 223-227  
 thiocarbanidin in, 78 570-575  
 thiosemicarbazone in, 62 144-148  
 thioureas, substituted  
   in guinea pigs, 70 130-138  
   in mice, 70 121-129  
 tissue fatty acids in resistance of rabbits to, 69 710-723  
 triiodothyronine and propyl thiouracil in, (Notes) 73 434-437  
 tubercle bacillus wax in, 76 752-760  
 tuberculin shock in mice, (Notes) 68 629-630  
 vaccines and immunity in, 71 228-248  
 viomycin in, 63 1-3, 4-6, 7-16, 17-24, 25-29, 30-35, 36-43, 44-48  
   acute and chronic toxicity, 63 44-48  
   *in vitro* effects against tubercle bacilli resistant to certain drugs, 63 36-43  
 virulence  
   in guinea pigs of isoniazid-resistant cultures, (Notes) 68 290-291  
   of human tubercle bacilli for guinea pigs, 73 266-275  
 extrapulmonary  
   pathogenesis of forms of, 62 (Supplement, July 48-67)  
   and pulmonary, PAS in, 61 613-620  
   suppurative, streptokinase-streptodornase in, 71 1-11  
 fashionable in 1759, (correspondence) 80 110  
 fatal, produced by BCG, (correspondence) 73 301-305  
 Fibreglas®-plastic dust, influence on, 78 512-523  
 fibrocaseous, isoniazid in, sputum culture and microscopy during treatment, 70 349-359  
 future problem of, program for control of, 80 (Supplement, October 117-137)  
 gastric, 61 116-130

## gel

-diffusion precipitation techniques in, 77 450-461  
 -diffusion tests in, 80 886-894  
 -double diffusion test for, 80 153-166  
 genital  
   female, (editorials) 75 501-505, (ATS) 524-527  
   transfer via semen, (case reports) 69 618-624  
 genitourinary  
   streptomycin treatment of, 61 518-524  
   transmission of, (correspondence) 75 153-156  
 in German population, U S Zone of Germany, 59 481-493  
 global eradication of, 80 (Supplement, October 138-139)  
 "good chronic case" of, (correspondence) 66 381  
 in Hawaii, 68 839-862  
 of the heart, 62 390-402  
 hemagglutination  
   reaction  
     in children, 70 139-148  
     in diagnosis of, 64 71-76  
 test, 62 121-127, 223-226  
   complement-fixation modification (Mallard), (Notes) 66 621-622  
   hemolytic, 66 594-600  
   modification in, 65 194-200  
 hematogenous, acute, in pregnancy in patient with tuberculous salpingitis, (case reports) 68 253-262  
 hepatic  
   hypokalemia in, (case reports) 68 136-143  
   and sickle-cell anemia, (case reports) 67 247-257  
 histoplasmin sensitivity in, 78 667-681  
 in Hong Kong, 76 215-224  
 hospitals  
   and home in, including chemotherapy of, 80 (Supplement, October 23-45)  
   rehabilitation and occupational therapy in, (correspondence) 79 680  
   vocational rehabilitation, justification of, 80 59-64  
 host resistance, relation of amino acids to, 66 378-380  
 in humans  
   alpha-ethyl-thioisonicotinamide in, antituberculosis effectiveness of, 79 6-18  
   cycloserine in, (Notes) 74 121-127  
   kanamycin in, 79 72-77  
   natural history of, 79 19-30  
 immunity, (editorials) 74 117-120  
 inhibition by chemoprophylaxis, 74 541-551  
 mechanism, relationship to pathologic changes, clinical symptoms, and therapeutic measures, (editorials) 68 933-937  
 and vaccines, 71 228-248



*Tuberculosis, cont*

- immunopathology of, 74 (Supplement, August 60-74)
- implications of changing morbidity and mortality rates from, 61 39-50
- in infancy and childhood, (case reports) 70 161-165, 73 422-433
  - cortisone and corticotropin in, 74 (Supplement, August 209-216)
  - incidence of, (Notes) 74 149-151, (correspondence) 80S-809
- infection
  - air-borne, in rabbits, 73 315-329
    - evaluation of method and its use in pathogenesis of tuberculosis, 61 765-797
  - constitutional factors in resistance to, 59 168-185, 186-197, 198-218
  - difference in response of four strains of mice to immunization against, (Notes) 80 753-756
  - and illness, 71 885-888
  - among Indian tribes, 72 35-52
  - in infancy, (Notes) 74 149-151, (correspondence) 80S-809
  - by injection of BCG, (correspondence) 72 869-870
  - murine, with *B abortus* and *M tuberculosis*, 73 251-265
  - mycobacterial, heterologous and homologous immunity in, 76 76-89
  - with streptomycin-resistant organisms, (case reports) 61 881-882
- influence on methylene blue reduction time of serum and heat coagulation value of plasma, (Notes) 70 907-909
- inoculation, after antityphoid vaccine, 71 465-472
- intestinal
  - chemotherapy as prophylaxis in, 64 430-441
  - PAS in, 61 621-642
  - streptomycin in, 60 576-588
- iodine in, (correspondence) 66 765-777
- isoniazid
  - cycloserine in, 75 553-575
  - pyrazinamide in, hepatotoxicity of, 80 371-387
  - serum concentrations and hemoglobin and methemoglobin values in, (Notes) 68 286-289
- among Jews, 67 85-93
- laboratory, routine, semi-synthetic autoclavable medium for, (Notes) 73 788-792
- lesions, relapse of, during and after chemotherapy, 80 (Supplement, October 47-71)
- lymphatic, 76 811-831
  - in children, enzymatic debridement of, 76 588-600
  - complications, 70 610-622
  - in neck, axilla, and groin, 73 229-238
  - treatment in accessible nodes, (editorial) 64 691-694
- mediastinal, 71 635-667
  - manifested by pericarditis, osteochondritis, and bronchoesophageal fistula, (case reports) 79 238-243
- in medical students at University of Maryland, 79 746-755
- meningeal
  - in adults, chemotherapy of, 68 912-925
  - in children, thiazolsulfone in, 61 159-170
- isoniazid in, 66 391-415
- in New York City, (Notes) 77 359-363
- survival rate (1948-1955) in armed forces, 76 360-369
- mental aspects of, 62 532-538
- miliary, 61 138-144, 68 636-653, 77 605-622
  - in adults, chemotherapy of, 68 912-925
  - agranulocytosis in, 59 317-324
  - cardiac involvement in, (case reports) 68 771-774
  - in children
    - in New York City, (Notes) 77 359-363
    - streptomycin-thiazolsulfone in, 61 159-170
  - chronic, 62 549-554
  - icterus in, (case reports) 66 77-85
  - isoniazid in, 66 391-415
  - lupus erythematosus cells in, (case reports) 74 112-116
  - with meningitis and leukemia, (case reports) 70 509-517
  - and pregnancy, 62 209-212, (case reports) 68 253-262
  - survival rate (1948-1955) in armed forces, 76 360-369
  - treated with streptomycin, (case reports) 60 514-519
  - in vitro* susceptibility of tubercle bacilli in, 74 (Supplement, August 232-240)
- minimal, streptomycin in, 65 547-571
- morbidity
  - in mental patients and general population, 70 32-48
  - trend, 67 279-285
- mortality
  - in mental patients and general population, 70 32-48
  - in New York City, (Notes) 77 516-518
  - in Puerto Rico since 1950, (Notes) 70 1099-1101
  - among residents of large cities (1947-1949), 66 109-116
  - among World War II veterans (1953-1954), (Notes) 73 966
- movement, accomplishments and opportunities, 65 221-234

*Tuberculosis, cont*

of myocardium, (case reports) 74 99-105  
 heart block change in, (case reports) 65 332-338  
 natural history of, in humans, longitudinal observations imperative, (editorials) 80 100-107  
 among the Navajo, 80 200-206  
 in neonatal period, 77 418-422  
 nephrectomy, partial, for, 66 744-749  
 noninfectious, chemotherapy in, to prevent relapse, (correspondence) 80 108  
 nonreactive, (case reports) 76 144-151, 79 362-370  
 in nurses, pathogenesis of, 60 305-331  
 and nutrition, 64 381-393  
   in adolescents, 74 (Supplement, August 173-183)  
 ocular  
   adrenal hormones in, 66 175-187  
   in rabbits, 64 197-206, 207-217  
     corticotropin effect on, in decreasing dosages, (Notes) 69 1051-1053  
     streptomycin-isoniazid and somatotrophic hormone effect on course of infection, 69 1016-1021  
 omental, pathogenesis of, 73 362-370  
 pain threshold in, 66 449-456  
 paper electrophoresis in  
   as a progress index in, (Notes) 76 892-895  
   study of patients with, (Notes) 75 99-1002  
 para-aminosalicylic acid for, 61 226-246  
   preparations in, 78 899-905  
   salt of isoniazid in, (Notes) 78 637-643  
   -sodium salt, administered subcutaneously, 64 557-563  
 pathogenesis of, shown in omental spreads, 73 362-377  
 patient(s)  
   attitude, evaluation of, 67 722-731  
   discharged, physical, psychologic, vocational, and socioeconomic status of, 69 153-163  
   hospitalized, adjustment on different wards, 79 273-283  
   leaving against medical advice, personality characteristics of, 67 432-439  
   nonhospitalized, 69 26-36, 75 41-52  
   rehabilitation of, (correspondence) 80 111-112  
   surgery refusal in, 77 311-322  
 pericardial, 61 845-861  
 peritoneal, 61 845-861  
 pleural, 61 845-861  
 and pneumococcosis, 3,3',5-triiodo-L-thyronine in survival time of mice with, 79 339-343

precipitin test for carbohydrate antibodies in, (correspondence) 59 710-712  
 prevalence, tuberculin conversion rates as indication of, 69 227-233  
 primary  
   and antimicrobial therapy  
     in children, 69 682-689, 73 305  
     and prognosis of, (correspondence) 70 535-536  
 in children  
   bronchoscopy in, 74 (Supplement, August 267-278)  
   segmental atelectasis in, 79 597-605  
   segmental lesions in, 79 756-763  
   value of follow-up studies, 64 499-507  
   of faucal tonsil, (case reports) 69 612-617  
   systematic treatment of, 74 (Supplement, August 191-196)  
   tubercle bacilli in, late discharge of, 79 31-40  
 among prisoners, San Joaquin County (California), 73 882-891  
 probable, and steatorrhea, with hypogammaglobulinemia, (case reports) 74 773-782  
 prophylaxis, in children, 74 (Supplement, August 75-89)  
 protein serum concentrations in, electrophoretic studies of, 68 372-381  
 psychologic aspects of, (editorial) 67 869-873  
 in psychotic patients, 59 289-310, (editorials) 68 782-785  
   collapse therapy in, 67 232-246  
 in Puerto Rico, 67 132-153  
 pulmonary  
   active, minimal, "modified" bed rest in, 61 809-825  
   with Addison's disease and histoplasmosis, (case reports) 72 675-684  
   adrenocortical function in, 64 630-644, 66 364-372  
 advanced  
   after-history of, 70 995-1008  
   outcome after 15 to 25 years, 72 487-501, 502-512  
   viomycin in, 70 812-840  
 aerial dissemination of, 76 931-941  
 after-history of, method of evaluation, 69 37-49  
 ambulation and chemotherapy in, 70 1030-1041, (correspondence) 71 602-603  
 amithiozone in, 64 170-181, 65 692-708  
 angiography, 71 810-821  
 antimicrobial therapy *See* chemotherapy, below  
 aureomycin in, 59 624-631  
 bed rest and physical activity in recovery from, 75 359-409

*Tuberculosis, pulmonary, cont*

bronchial disease in lungs resected for, 68 657-677

bronchial preoperative biopsy in, 78 839-847  
and bronchogenic carcinoma, 61 369-386,  
73 853-867

bronchography, 64 394-407, 70 274-284  
preceding surgery, 77 561-592

bronchspirometry  
before and after resection and lobectomy,  
75 710-723  
of pulmonary function after decortication,  
66 509-521

C-reactive protein in, (Notes) 74 464-467

chemotherapy of, 69 1-12  
comparison of effect of four variables,  
72 718-732  
high doses of isoniazid with PAS and  
pyridoxine, (Notes) 78 773-784  
isoniazid, streptomycin, and PAS compared  
as two drug regimens, 72 756-784  
lesions after prolonged use, 71 165-185  
phenomenon of open-cavity healing, (edi-  
torials) 71 441-446  
prolonged indefinitely, 70 219-227

streptomycin  
and isoniazid with PAS and pyridoxine,  
(Notes) 78 773-784  
and PAS, three regimens compared,  
72 733-755  
and systemic blastomycosis, (case reports)  
68 615-621

chronic  
effect of artificial pneumoperitoneum on  
ballistocardiogram, 66 52-57  
fibrocaceous, relapse rates after, (Notes)  
71 302-304  
fibroid, potassium iodide and PAS in,  
64 77-80  
hepatic damage in, 72 71-90  
massive dose isoniazid with pyridoxine in,  
(Notes) 78 474-477  
treatment-failure, cycloserine and high-  
dose isoniazid in, (Notes) 80 269-273

coexistent with coccidioidomycosis, 67 477-  
489

coexistent with fungal disease, (case reports)  
72 667-674

comparison of isoniazid, streptomycin, and  
streptomycin-PAS in, (Notes)  
66 632-635, (Notes) 67 108-113

complicated with spontaneous pneumothorax,  
74 351-357

corticotropin, PAS, and streptomycin in,  
66 542-547

and cycloserine  
psychologic effects of, (Notes) 73 438-441

-pyrazinamide in, (Notes) 76 1097-1099,  
78 927-931

-viomycin in, (Notes) 79 90-93

decortication of lung in, 59 30-38, 60 288-304

development over prolonged period of time,  
66 1-15

diagnosis, tracheal lavage and culture in,  
60 634-638

and dihydrostreptomycin, 62 572-581  
sulfate in, neurotoxicity of, 65 612-616

disposition and follow-up, 60 487-500

drug resistance in resections, 75 781-792

drug-treated, cystic cavities and, 77 221-231

effect of nontuberculous pulmonary inflamma-  
tion on, 59 68-75

emotional factors in, 62 428-433

in employees of tuberculosis hospitals, 66 16-  
27

empyema in, 59 601-618, 78 411-425

S-ethyl-L-cysteine in, (Notes) 74 142-144

exacerbation of, with special reference to  
allergy, (correspondence) 74 155-157

extraperiosteal Lucite plombage in, 68 902-911

and extrapulmonary PAS in, 61 613-620

gas mixing in, 74 343-350

in group continuously observed and period-  
ically re-examined, 66 1-15

healing  
of open cavity in, 73 944-955  
rate, with chemotherapy, 76 988-1001

hematogenous, cardiopulmonary function in  
patients receiving streptomycin,  
64 583-601

hemorrhage in, 62 324-330  
fatal, 60 589-603  
pneumonectomy for, 61 426-430

hepatic derangement in, 76 410-425

hinconstarch in, 73 219-228, 77 952-967

histologic study of blood vessels in resected  
lung, 64 489-498

in humans  
isoniazid serum concentrations and thera-  
peutic response in, correlation of,  
(correspondence) 80 108-110  
thiocarbanilide SU 1906 in, (Notes) 74 468-  
470

hydroxyethyl sulfone in, 68 103-118

hypopotassemia and hyponatremia in, during  
treatment with streptomycin-PAS,  
66 357-363

immobilization of lungs in, 66 261-270,  
(correspondence) 778-780

inactive, reactivation of, 73 31-39

incidence and significance of thromboem-  
bolism in, 61 826-834

indolent, diffuse, 71 503-518

infectivity of, related to sputum status,  
69 724-732

*Tuberculosis, pulmonary cont*

- influence of external factors on, 62 539-542
- intermittent positive pressure breathing in, 72 479-486
- international survey, (Notes) 73 128-133
- involving lower lobes, artificial pneumothorax in, 59 50-52
- iodized oil bronchography, 66 699-721
- and isoniazid, 65 429-442, (correspondence) 71 314-315, (Notes) 73 117-122
  - adrenal cortical function during treatment, 70 841-851
  - alone in, (correspondence) 70 924-925, 74 903-916
  - cystlike cavities during therapy, (Notes) 69 1054-1056
  - cycloserine in, (Notes) 79 87-89
  - and electrophoretic serum proteins, 70 334-343
  - high-dose, (Notes) 77 539-542
  - long-term, 70 228-265
  - pathology of lesions, 71 186-192
  - peripheral neuropathy in, (case reports) 68 458-461
  - streptovaricin, (Notes) 80 424-425, 431-433
  - treated, surgical pathology of, (Notes) 68 144-149
- and liver, clinical, functional, and needle biopsy study of, 63 202-209
- lower lobe, 59 39-49, 60 1-14
- lung function in, 79 474-483
  - bilateral resection for, 79 468-473
- lung immobilizer therapy in, (correspondence) 67 267
- mass roentgenography in, 60 466-482
- in medical and nursing students, 63 332-338
- minimal, 76 64-75
  - after-history of, 70 15-31
  - confined to apex of one lung, treatment of, 63 644-656
  - five-year follow-up, 73 818-830
  - in military personnel, 75 1-40
  - modified bed rest in, 67 401-420
  - rest and exercise in, 69 50-57
  - with and without chemotherapy, 73 818-830
- moderately advanced, after-history of, 71 519-528
- mouse test for, (Notes) 77 1005-1011, 1012-1016
- mouth wash-membrane filter cultures in, 71 371-381
- multiple drug therapy in, 76 540-558
- nasal swab cultures in, (Notes) 80 909-910
- new and untreated, isoniazid- and streptomycin-resistant tubercle bacilli in, (Notes) 74 293-296
- in New York State penal institutions, 61 51-56
- neomycin aerosol in, (Notes) 78 135-137
- noncavitary, isoniazid and isoniazid-PAS in original chemotherapy of, 80 641-647
- in noninfectious patient with cavity, resection for, 74 169-177
- open, transition to sarcoidosis, (case reports) 78 769-772
- oxytetracycline-streptomycin in, 66 534-541
- PAS in, (Notes) 73 117-122
  - treatment, 61 597-610
- para-isobutoxybenzaldehyde thiosemicarbazone in, failure of, (Notes) 68 791-793, 794-795, 796-798, 799-802
- pathology of, 61 543-555
  - lesions in, 71 (Supplement, March 1-244)
- peptic ulceration following surgery, 74 358-366
- in persons observed from childhood, 75 885-896
- in persons over forty, 59 469-480
- phrenic nerve interruption in, 60 168-182, 183-188
- physical activity during convalescence, energy cost of, 71 722-731
- plasma viscosity and erythrocyte sedimentation determinations in, 69 595-598
- pneumonectomy in, 77 73-82, 260-270, 78 822-831
- pneumoperitoneum in
  - effect of liver function, 65 589-595
  - effect on respiration, 70 672-688
  - with phrenic paralysis for, 61 323-334
  - with streptomycin and PAS in, 69 963-967
- post-primary, (correspondence) 73 598-600
- frequency according to pulmonary arterial pressure, 78 536-546
- prediction of relapse, 73 472-484
- and pregnancy, (case reports) 66 86-89
  - after pneumonectomy for, 78 563-569
- preresection drug therapy in, 79 41-46
- with primary pulmonary carcinoma, 79 134-141
- progression of, 66 666-679
- protective antibody in, passive transfer of, 76 256-262
- protein hydrolysate in, 59 511-518, 519-538
- psychosocial factors in, 75 768-780
- psychosomatic study of, 71 201-219
- after pulmonary excision for nontuberculous disease, 61 835-844
- pyrazinamide, 65 523-546, (case reports) 69 443-450
  - alone and in combination with streptomycin, PAS, or isoniazid, 60 413-422
  - isoniazid, 69 319-350, (Notes) 70 743-747
  - low dosage, 74 400-409
  - or PAS, (Notes) 79 102-104
- Rasmussen's aneurysm in, 60 589-603
- of recent origin, isoniazid in, 71 841-859

*Tuberculosis, pulmonary, cont*

- recrudescence, early, in, 65 673-691
  - recurrent laryngeal nerve paralysis as complication of, (case reports) 65 93-99
  - reinfection and apical localization
    - blood layering in dog heart, 70 570-576
    - of experimental emboli, 70 557-569
    - stream flow theory, 70 547-556
  - relapse
    - factors in, 72 613-632
    - and mortality, 70 601-609
    - with and without chemotherapy, 79 612-621
  - relation of
    - to bronchogenic carcinoma, 64 620-629
    - to nutritional status, 62 58-66
  - resection, 59 10-29, 71 349-360, 73 79-98, 74 29-41
    - bilateral, 68 885-901, 74 367-375, 75 259-265
    - bronchial ulceration after, 69 84-91
    - of bronchus, 74 874-884
    - drainage following, (Notes) 69 636-637
    - in Hawaii, 80 6-11
    - of isoniazid-treated lesions, 70 102-108
    - of post-treatment residual lesions, 73 165-190
      - in resected specimens, 71 830-840
      - segmental, 69 554-565, 70 285-295
      - simultaneous, and thoracoplasty, 65 159-167
    - streptomycin-protected in, 67 22-28
  - residual volume, bilateral, determination of, 78 376-390
  - respiratory function impairment in, 71 333-348
  - re-treatment with viomycin, (Notes) 72 843-845
  - roentgenography
    - mass, 65 451-454
    - serial, interpretation of, 64 225-248
    - spread of, during sanatorium residence
      - before use of prolonged chemotherapy, 68 863-873
    - and surgical findings, comparison of, (Notes) 71 452-456
    - unreliability of diagnosis by, 69 566-584
  - serology of, 68 739-745
  - serum enzymes in, (Notes) 79 251-252
  - serum gamma globulins in, (correspondence) 61 893-894
  - serum protein fractions, electrophoretic and chemical, in, 67 299-321
  - simian, isoniazid in, 74 (Supplement, August 138-153)
  - streptomycin, (Notes) 73 117-122
    - dihydrostreptomycin in, comparison of, 68 229-237, 238-248
    - first clinical trial, (case reports) 71 752-754
    - five-year outcome, 71 193-200
    - intermittent regimens, analysis of patients treated with one or two grams every third day, 63 275-294
    - once weekly in, 69 980-990
    - with other forms of therapy for, (editorials) 60 264-268
    - PAS in, (Notes) 72 242-244
      - intermittent regimens, comparison with daily dosage schedules, 63 295-311
    - and pneumothorax in, 59 539-553
    - refractory, pneumonectomy and streptomycin for, (case reports) 66 605-614
    - streptomycyclidene isonicotinyl hydrazine sulfate, in, 70 701-713
    - streptovaricin alone in, (Notes) 80 426-430
    - surgery in, 73 690-703, 80 207-215, 80 (Supplement, October 95-115)
      - complicated by Horner's syndrome, 67 94-100
    - electrocardiogram in, 65 443-450
    - indications for, 73 191-218
    - management of, (Notes) 76 902-905
    - total statistics in, 68 874-884
  - suture ligation and partial thoracoplasty in, 70 61-70
  - testosterone in, 68 165-176
  - thiocarbanidin-isoniazid in, (Notes) 80 590-593
  - thoracoplasty in, 59 113-127, 60 273-287, 62 645-653
    - failure as indication for resection in, 62 434-438
    - primary, 78 832-838
    - in ten-year follow-up, 69 930-939
  - three-year follow-up study on 202 cases treated with streptomycin, 62 563-571
  - tracheal lavage and culture in diagnosis for, 60 634-638
  - tuberculin
    - hypersensitivity in, (Notes) 74 474
    - skin reaction in, 78 399-402
  - vascular changes in lungs in, 75 410-419
  - verazide in, 78 251-258
  - viomycin, 69 543-553
  - vocational rehabilitation in, (editorials) 78 647-650
  - widespread, in 19-day-old infant, Promizole®-streptomycin in, 61 747-750
- rates, among prisoners, 74 590-596
- reactors, finding of, 71 406-418
- rehabilitation in Philadelphia (Pennsylvania), 62 190-208
- reinfection, streptomycin-resistant tubercle bacilli inoculation in, 74 258-276
- relationship of immunity mechanism to pathologic changes, clinical symptoms,

*Tuberculosis, pulmonary cont*

- and therapeutic measures in, (editorials) 68 933-937
- renal
  - calcification in, (case reports) 71 437-440
  - chemotherapy of, urine cultures during, 70 149-154
  - experimental studies on pathogenesis and prognosis of, 61 508-517
  - roentgenographic classification of, 67 604-612
- research
  - cooperative, clinical, (editorials) 68 263
  - cost, in United States, 60 393-405, 527-531
- resistance, 77 436-449
  - concept of, 62 (Supplement, July 3-12)
  - in guinea pigs vaccinated with BCG, 60 547-556
  - humoral factors in, 76 90-102, 78 884-898
- respiratory function in *See also* Pulmonary function and Respiratory function and in other chronic lung diseases (Soviet translation), 79 142-151
- revisited, a schema for, 78 333-345
- risk of developing among children of tuberculous parents, 70 1009-1019
- sanatorium(s)
  - histoplasmosis in, 73 609-619
  - place of laboratory in, (editorials), 73 291-293
- scientific appraisal of new drugs in, (editorials) 61 751-756
- among Selective Service registrants, 60 773-787, 80 795-805
- serologic test
  - new, 64 675-681
  - value of absorption in, (Notes) 66 762-764
- serology of, hemagglutinin adsorption in, 67 657-664
- of serosal surfaces, 61 845-861
- and sickle-cell anemia, 65 735-743
- skeletal
  - in children with primary and miliary tuberculosis, 75 897-911
  - treatment of, 74 (Supplement, August 124-133)
- somatotrophic hormone in, (correspondence) 71 319-320
- in South America, (correspondence) 67 676-678
- of spleen, with polycythemia, (case reports) 60 660-669
- sterility, female, in, (editorials) 70 1096-1098
- of stomach, 61 116-130
- streptomycin, 77 413-417
  - research project, 59 140-167
- stress and adrenocortical function, relationship with, 69 351-369
- in students, (Notes) 76 308-314
- studies in Muscogee County (Georgia), 73 157-164
- surgery in
  - combined with pyrazinamide-viomycin, 77 83-92
  - thoracic, major, full-term delivery following, 78 697-711
- survey-detected, ultimate fate of, 68 9-23
- survival of patients, 66 651-665
- susceptibility
  - familial, BCG as index of, 69 383-395
  - of normal and immunized mice to, relationship of sex to, (Notes) 80 750-752
  - in Taiwan (Formosa), 80 359-370
  - teaching in medical schools, (editorials) 60 140-142, 63 365-371
- therapy, 74 (Supplement, August 188-190)
  - immunity in, 78 499-511
  - rapidly effective, implications of, (editorials) 61 892
  - for 30 years in a municipal sanatorium, (editorials) 70 518-520
- thoracoplasty, preresection and postresection, in, 79 204-211
- thyroid in native resistance to, 79 152-179, 180-203
- tissue culture studies in resistance in, 79 221-231
- today and tomorrow, 67 707-721
- tracheal, 60 604-620
  - streptomycin for, 60 32-38
- tracheobronchial, 60 604-620
  - streptomycin for, 60 32-38
- treatment, 70 930-948, 72 1-11
- tuberculin-negative, 63 501-525, (correspondence) 64 468-469, 469-471
- tuberculin reactions during isoniazid treatment, 69 733-744
- undetected, in economic groups, 70 593-600
- unsolved problems in, 70 391-401
- urban reservoirs of (ATS), 79 687-689
- of urinary tract, uremia from, (case reports) 73 110-116
- vaccination against, 74 (Supplement, August 28-31)
  - with nonliving vaccines, 80 340-358, 495-509, 676-688
- views in perspective, 74 (Supplement, August 290-296)
- viomycin in, 69 520-542
- vitamin A in, 64 381-393
  - metabolism in, 72 218-227
- vocational rehabilitation in, (correspondence) 79 543
- and World Health Organization, (editorials) 64 218-222
- Tuberculostatic agents
  - guinea pig test for, 60 223-227
  - present in animal tissues, (Notes) 63 119
- Tuberculostatic factor in normal human urine, 73 967

- Tuberculostatic substance possessing lysozyme-like properties in serum, 64 669-674
- Tuberculous patient(s)  
 cardiac symptoms in, 62 (Supplement, July 98-103)  
 at home, 76 1049-1062  
 hospitalized, personality and behavior in, 76 232-246  
 and personnel pressure, (correspondence) 76 912-914  
 psychiatric evaluation of, (correspondence) 74 807  
 rating of, 70 483-489  
 rehabilitation of, in Philadelphia (Pennsylvania), 62 190-208
- Tularemia, lung abscess in, (case reports) 65 627-630
- Tumor(s)  
 adenoma  
 bronchial, 75 865-884  
 and supernumerary bronchus, (case reports) 75 326-330  
 adenomatosis, pulmonary, (case reports) 60 258-263  
 alveolar, (case reports) 60 788-793, 61 131-137  
 carcinoma  
 alveolar cell, 79 502-511  
 pulmonary, 62 594-609  
 bronchiolar, (case reports) 78 632-636  
 terminal, with inflammation and fibrosis, 76 559-567  
 bronchogenic  
 with carcinoma of larynx, (case reports) 74 438-440  
 as a differential diagnostic problem in pulmonary disease  
 I from major bronchi without secondary infection, 63 176-193  
 II *ibid*, with secondary infection, 63 255-274  
 III peripheral from minor bronchi and bronchioles, 63 399-416  
 and pneumonia in adults, 76 47-63  
 preclinical, 69 164-172  
 in relation to calcified nodules in lung, 66 151-160  
 and silicosis, (case reports) 76 1088-1093  
 and thrombocytopenic purpura, (case reports) 67 509-513  
 tuberculoma of lung simulating, 61 431-435  
 tuberculosis, bronchiectasis, and calcification as related to, 64 620-629  
 and tuberculosis, pulmonary, 61 369-386, 73 853-867  
 of larynx, with bronchogenic carcinoma, (case reports) 74 438-440  
 of lung, primary, with pulmonary tuberculosis, 79 134-141  
 chest lesions, asymptomatic and circumscribed, 62 512-517  
 "coin" lesions of lung, (Notes) 73 134-138  
 endothelioma of pleura, case reports with surgical extirpation, 63 150-175  
 hamartoma, endobronchial, (case reports) 80 65-70  
 hemangiopericytoma of lung, (case reports) 77 496-500  
 hemangio-sarcomatosis, generalized, erroneously considered generalized tuberculosis, 61 257-262  
 hematoma, extrapleural, complicating extrapleural pneumothorax, streptokinase-streptodornase in, 63 547-555
- leukemia  
 alveolar-capillary block due to, (case reports) 80 895-901  
 pulmonary involvement in, 80 833-844  
 lymphosarcoma, pulmonary, with alveolar-capillary block and coccidioidomycosis, (case reports) 78 468-473  
 malignancy, pulmonary, cytologic diagnosis of, 61 60-65  
 mediastinal, 60 419-438  
 cardiospasm simulating, (case reports) 63 597-602  
 mesothelioma, pleural, (case reports) 71 280-290  
 diffuse, malignant, (case reports) 78 268-273
- neoplasms  
 and mediastinal cysts, in children, 74 940-953  
 pulmonary  
 and eosinophilia, (case reports) 75 644-647  
 mass surveys for, 62 501-511
- neoplastic disease, meningeal, simulating tuberculous meningitis, (case reports) 69 1029-1036
- neuroma, acoustic, tuberculoma of cerebello-pontine angle simulating, (case reports) 63 227-229
- nodules, pulmonary, solitary, found in survey, 79 427-439
- papilloma of bronchus, (case reports) 78 916-920
- papillomatosis, bronchial and tracheal, (case reports) 71 429-436
- pulmonary  
 diagnosis and treatment, 59 353-363  
 solitary, 63 252-254
- reticulum cell sarcoma, cryptococcal and tuberculous meningitis in, (case reports) 78 760-768
- thymoma  
 cystic, and tuberculoma, possible confusion between, (case reports) 70 155-160  
 malignant, with myasthenia gravis, (case reports) 72 381-385

Tween<sup>†</sup>

- albumin liquid medium, in differentiation of tubercle bacilli, (Notes) 79 810-812
- inhibitory action on D-29 mycobacteriophage inhibited by serum albumin, (Notes) 80 113-114
- 80 and serum, effect on phage, 77 131-145

## U

## Ulcer(s)

- BCG induced, healing effect of isoniazid on, 74 7-11
- peptic
  - and emphysema, 80 (Supplement, July 155-156)
  - after surgery for pulmonary tuberculosis, 71 358-366

Ulceration, bronchial, after pulmonary resection for tuberculosis, 69 84-91

Ultrafiltration apparatus, (Notes) 63 718-720

Ultrasonics, exposure to, in comminution of mycobacteria, (correspondence) 76 914-915

Ultraviolet, H<sub>i</sub> Intensity, for sterilization, (Notes) 71 157-158

Umbradil, in bronchography, 68 760-770

United States, irregular discharge in, (correspondence) 69 847-850

University of Maryland, tuberculosis in medical students at, 79 716-755

Urease activity in mycobacteriaceae, (Notes) 65 779-782

Urecholine in gastric dilatation following phrenic interruption, 62 331-332

## Uremia

- with sarcoidosis, (case reports) 60 236-248
- from urinary tract tuberculosis, (case reports) 73 110-116

Urethane of beta-methylcholine See Urecholine

## Urine

- human
  - normal, tuberculostatic factor in, (Notes) 73 967
  - spectrophotometric determination, of PAS, (Notes) 64 577-578
- pancreatin-quaternary ammonium treatment of, 74 616-621
- PAS in, 76 1071-1078
- tests
  - for detection of isoniazid, (Notes) 80 904-908
  - simple paper strip, for PAS, (Notes) 80 585-586
- tuberculininhibitory activity of role of ascorbic acid in, 69 406-418
- from tuberculous patients, for amino acid metabolism study, 76 867-870

## U S S R, translation, of review

- from Puzik and Uvarova, 79 497-501
- from Stepanyan, 79 112-151

## V

## Vaccination

- antituberculosis, with nonliving vaccines, (Notes) 77 719-721

## BCG

- as index of familial susceptibility to tuberculosis, 69 393-395
- in Panama, (Notes) 67 522-525
- purified tuberculin fraction, from unheated cultures in testing, (Notes) 69 300-303
- in sarcoidosis, 62 408-410
- in silicosis, 62 155-174
- in Sweden, (correspondence) 79 678-679
- and vole, 71 (Supplement, August 43-50)
- of mice, against *C. immitis*, 74 245-248
- against tuberculosis, 74 (Supplement, August 28-31)
- with nonliving vaccines, 80 340-348, 495-509, 676-688

## Vaccine(s)

- antityphoid, cutaneous and lymphatic tuberculosis after, 71 465-472
- assay, tuberculin reaction in, 66 351-356
- BCG See BCG
- from gamma-irradiated *M. tuberculosis* and *Br. suis*, (Notes) 79 374-377
- in immunization against experimental tuberculosis, 71 228-248
- irradiated, antituberculosis, (Notes) 75 987-991
- and BCG in experimental tuberculosis in guinea pigs, 67 341-353
- studies with, 62 418-427
- nonliving, in antituberculosis vaccination, 77 719-724, 80 340-348, 495-509, 676-678

Vascular changes in lungs in pulmonary tuberculosis, 75 410-419

Vena caval obstruction due to histoplasmosis, (case reports) 77 848-857

Ventilagram, expiratory, 80 724-731

Ventilation See also Pulmonary function

in chronic pulmonary emphysema, 74 210-219, 220-228

and respiratory gas exchange, mechanical respirators in, 80 510-521

effect on antituberculosis activity of thioethyl compounds, 74 68-71

helium-dilution method in study of, 79 450-456

lobar, in man, 73 330-337

measurements

in coal miners, 59 270-288

by Ventube, 75 303-318



Ventilation, *cont*

- mechanics, in emphysema, 80 (Supplement, July 118-120)
- numerical expression of functionally effective portion, 62 17-28
- Ventilatory capacity, tests
  - index of expiratory force in, 78 692-696
  - maximal midexpiratory flow, 72 783-800
- Ventilatory efficiency, nitrogen clearance in, 72 165-178
- Ventilatory function, tests
  - in sanatorium or clinic, 60 149-167
  - value of, in evaluating patients for thoracoplasty, 63 76-80
- Ventilatory obstruction, maximal expiratory flow test for, 78 180-190
- Venturi principle, in measuring ventilation, 75 303-318
- Verazide
  - pharmacology, 76 346-359
  - in pulmonary tuberculosis, 78 251-252
  - and related hydrazones, antituberculous activity of, 76 331-345
- Vessel(s)
  - in pulmonary emphysema, 80 (Supplement, July 67-91)
- Veterans Administration
  - Armed Forces, cooperative studies of tuberculosis
    - antimicrobial therapy in primary tuberculous pleurisy with effusion, 74 897-902
    - resection in (1952-1955), 73 960-963
    - survival among patients with military and meningeal tuberculosis (1948-1955), 76 360-369
  - Army and Navy, cooperative study
    - April 1, 1949, to January, 1951, 72 718-732
    - February 1, 1951, to January, 1952, 72 733-755
    - August, 1952, to September, 1954, 72 756-782
  - streptomycin regimens, study of, July 1946-April 1949, 60 715-754
- Viability test, for suspensions of tubercle bacilli, (Notes) 66 95-98
- Viomycin
  - activity
    - antimicrobial, 63 7-16
    - against mycobacteria, 63 1-3
    - against *M. tuberculosis* and other microorganisms *in vitro* and *in vivo*, 63 17-24
  - anaphylaxis, (case reports) 75 135-138
  - cycloserine, in pulmonary tuberculosis, (Notes) 79 90-93
  - effect
    - on plasma electrolytes, 68 541-547
    - on renal function, 68 541-547
    - on tubercle bacilli, phase contrast and electron-microscopic studies of, (Notes) 73 296-300

- in experimental tuberculosis, 63 1-48
  - acute and chronic toxicity, 63 44-48
  - effects, *in vitro*, against tubercle bacilli resistant to certain drugs, 63 36-41
- pyrazinamide, in surgical therapy of tuberculosis, 77 83-92
- streptomycin, isoniazid, and streptomycin-diene isonicotinyl hydrazine in experimental mouse tuberculosis, (Notes) 68 292-294
- toxicity in humans, 63 49-61
- in tuberculosis, 69 520-542
  - pulmonary, 69 543-553
  - advanced, 70 812-840
  - re-treatment, (Notes) 72 843-845
- Viruses
  - infections, of respiratory tract, 80 315-325
  - influenza, Asian, in 1957, pathology of, 79 440-449
- Vital capacities, total and timed, for bedside and office use, 80 724-731
- Vitamin A
  - metabolism, in tuberculosis, 72 218-227, (correspondence) 73 603-604
  - in tuberculosis, 64 381-393
- Vitamin analogues, inhibition of growth of tubercle bacilli by, 62 (Supplement, July 34-47)
- Vitamin E deficiency, isoniazid in, 80 223-231
- Vocal cord paralysis, 73 52-60
- Vole and BCG vaccinations, 74 (Supplement, August 43-50)

## W

- Washington, D. C., roentgenographic survey in (1948), 66 548-566
- Wax of tubercle bacillus, immunogenicity for mice, 80 216-222
- Wegener's granuloma of the lung, 78 21-37 *See also* Pneumoconioses
- Welders *See* Pneumoconioses
- Will Ross Medal (1954), 72 566-568
- Win 5211 *See* 5-Heptyl-2-thiohydantoin
- World Health Organization, and tuberculosis, (editorials) 64 218-222

## X

- X-ray *See* Roentgenography
- X-ray therapy *See* Radiation therapy

## Y

- Yeasts and pathogenic fungi, tuberculostatic properties of culture filtrates of, (Notes) 66 623-625

## Z

- Zephiran® *See* Benzalkonium chloride
- Zinc, traces of, in glycerol, (Notes) 74 145-146
- Zone electrophoresis, in starch gels, (Notes) 78 932-933





THIS NUMBER CONTAINS ABSTRACTS OF TUBERCULOSIS

Vol. XLIV

JULY, 1941

No. 1

# THE AMERICAN REVIEW OF TUBERCULOSIS

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## CONTENTS

SEIBERT, FLORENCE B	History of the Development of Purified Protein Derivative Tuberculin	1
SEIBERT, FLORENCE B, AND GINN, JOHN T	Tuberculin Purified Protein Derivative Preparation and Analyses of a Large Quantity for Standard	
COURRAND, ANDRE, AND RICHARDS, DICKINSON W., JR	Pulmonary Insufficiency I Discussion of a Physiological Classification and Presentation of Clinical Tests	26
SAVACOL, J. WOODROW, AND CHARR, ROBERT	Thrombosis of the Pulmonary Artery	42
BOESSEVAIN, C. H., AND CHAPMAN, F. N.	Leucocyte Count and Recovery from Tuberculosis Correlation of Neutrophile Polynuclears, Lymphocytes, Monocytes and the Medlar Index with Recovery from Tuberculosis at Different Altitudes above Sea Level	55
KRUCKER, ALFRED L., AND PERIBERE, HARRY J.	Laboratory Procedures in Intestinal Tuberculosis	73
COHEN, SAMUEL	Influence of Posture on the Intrapleural Pressure in Artificial Pneumothorax	75
PERMAN, H. HARPIS, BROWN, HERMAN, AND RAIZIS, GEORGE W.	With the assistance of Miss Anna Rule Chemotherapy of Experimental Tuberculosis	83
WISSE, F. ROBERT	Spontaneous Closure of Tuberculous Cavities A Roentgenological Study	92
KERESZTURI, CAMILL	Present Status of the Tuberculin Patch Test	94
CLINICAL AND LABORATORY NOTES		
KETTLKAMP, G. D., AND STANBRO, WILLIAM W.	Tuberculosis in Identical Twins	104
BOGGS, LAMM	Eye Color and Tuberculosis	110
OATWAY, W. H., JR	Fibrin Bodies in Pneumothorax	112
STEFANKIN, WILLIAM, JR	Try for Staining Tubercle Bacilli	115
DAVIES, ROBERTS, AND ROBB, CHARLES S.	Community Survey for Tuberculosis	118
Abstracts of Tuberculosis		1

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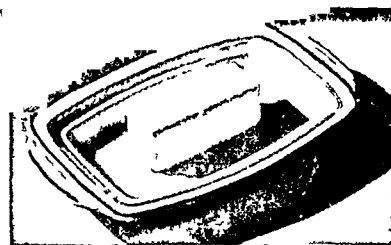
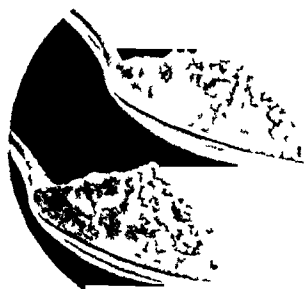
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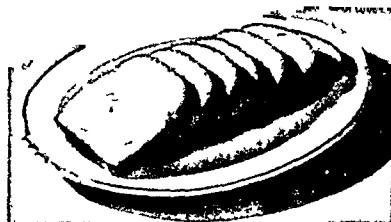
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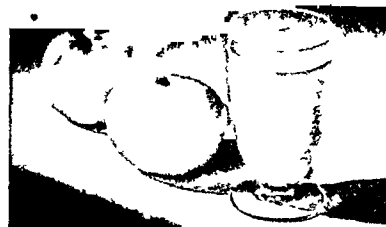
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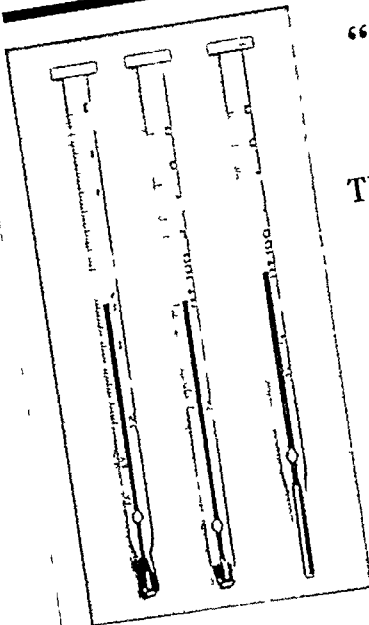
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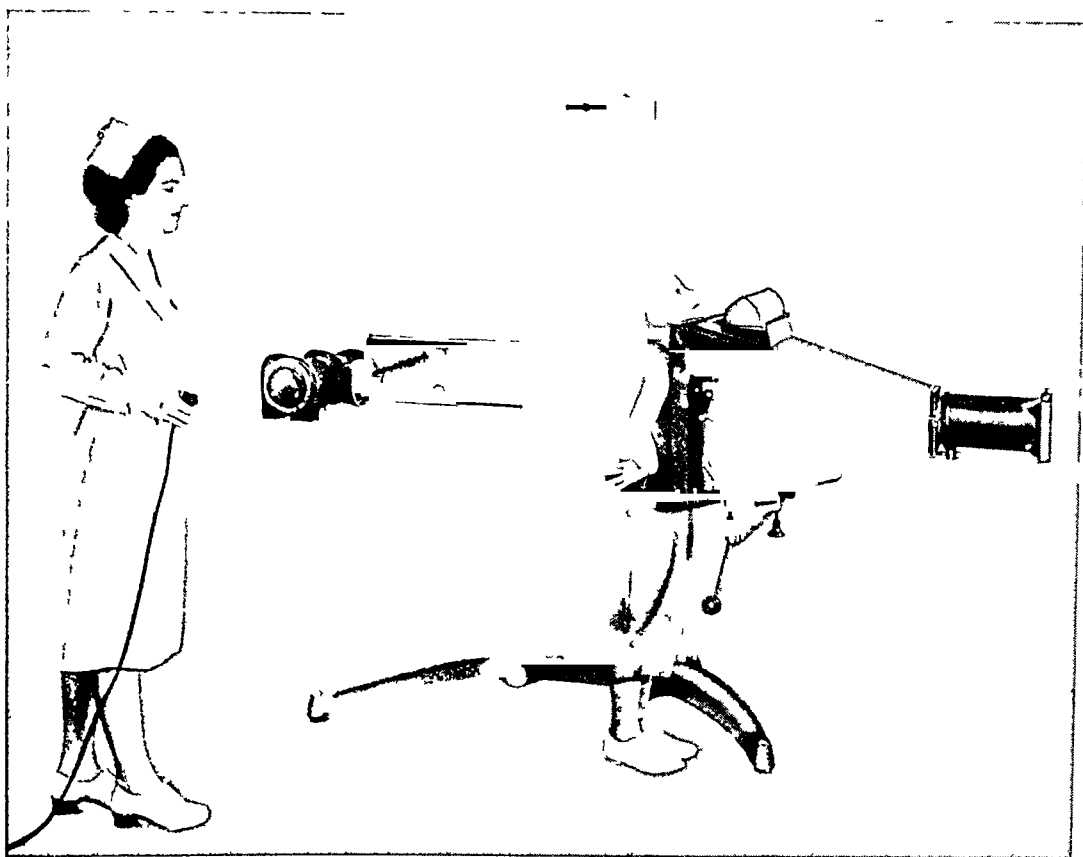
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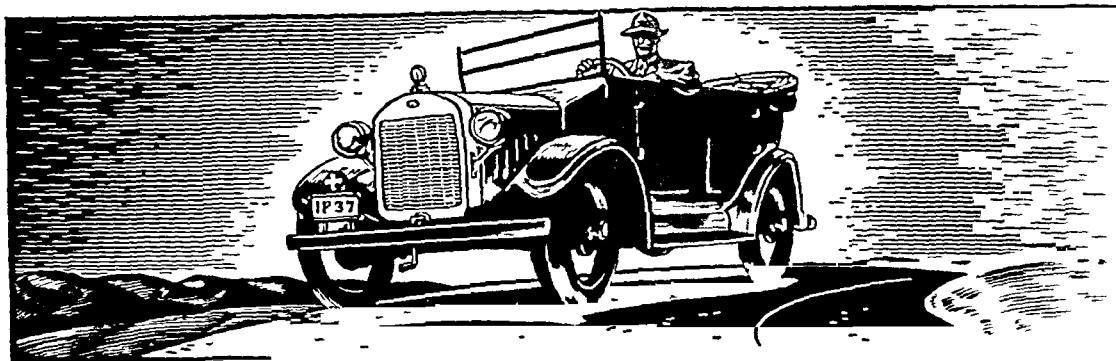
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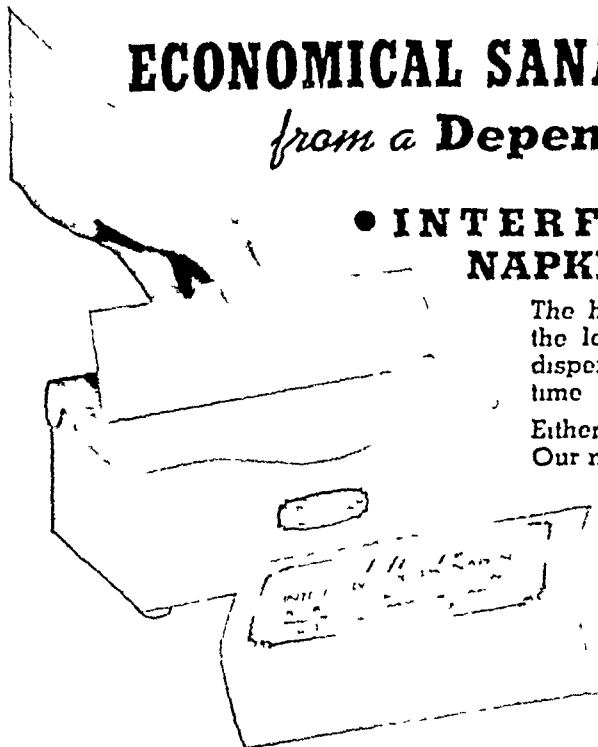
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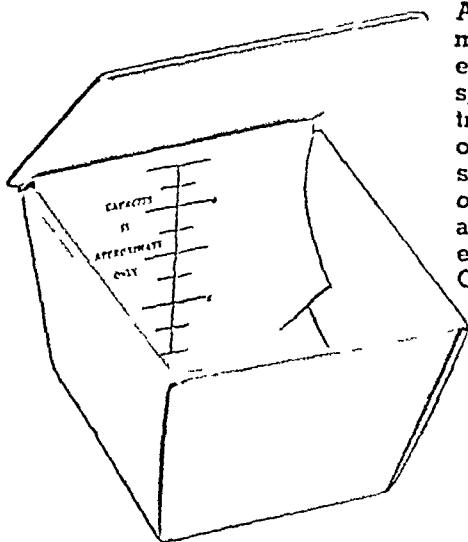
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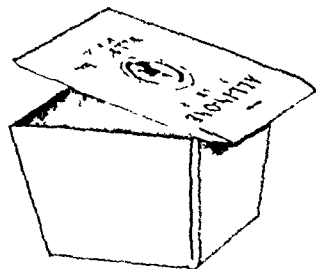
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# HISTORY OF THE DEVELOPMENT OF PURIFIED PROTEIN DERIVATIVE TUBERCULIN<sup>1 2</sup>

FLORENCE B SEIBERT

A request has been made for a short résumé of the methods of approach and the results that have led to the development of the Purified Protein Derivative of tuberculin. Much of the work to be reviewed was undertaken as supplementary to work reported in the literature, especially where it was desirable to confirm or reinvestigate a conclusion. No references will be given to the literature in this review, since they have been listed adequately in various reviews and also in the papers on the individual phases of the work. A general survey relating these investigations to previous work is in press in *Bacteriological Reviews*.

The experimental work to which reference is here made will therefore be only that which has been carried out under grants from the Committee on Medical Research of the National Tuberculosis Association in the laboratory of the author, with a large number of collaborators, chief among whom was Dr Esmond R Long. No attempt will be made to give details concerning any procedure, since they can be more accurately and satisfactorily obtained from the individual papers.

At the outset a most vital precedent for the entire research was established, namely, the use of a synthetic medium for growing the bacilli. The medium (Long's) adopted was one which contained no protein and only pure chemicals, such as asparagine, ammonium citrate, glycerol and inorganic salts. On this medium the bacilli grew well and produced a filtrate which was highly potent as a tuberculin.

The first question, whether the active principle is or is not protein, was considered from many angles and a summary of the results leading to the conclusion that it is protein, is given below. It will indicate the nature of experimentation used in the studies.

1 When protein appeared in the culture medium, there was also tuberculin activity in the medium.

<sup>1</sup> From the Henry Phipps Institute of the University of Pennsylvania, Philadelphia, Pennsylvania.

<sup>2</sup> Aided by grants from the Committee on Medical Research of the National Tuberculosis Association.

*Niedtzen, A. J. Tuberc. Abstr. (Engl.), 1932, Page 1-2, 11: 112. (L. F. B.)*

#### Temporary Paralysis of Intercostal Nerves.

The author describes the technique of injection of the local anesthetic into intercostal nerves, the object being to produce temporary paralysis of that portion of the chest. It is suggested that use of this procedure has indicated indications, especially in cases in which it is impossible to establish a pneumothorax and in which other cases. It is of use in cases of severe and obstinate hemothorax. It should be considered in early cases in which it is undecided whether pneumothorax is necessary and in cases too much to withstand other operative procedures.

*Treatment of Pulmonary Tuberculosis by Temporary Elimination of a Number of Intercostal Nerves, F. Tuck, J. Thorac. Surg., August, 1930, 3: 1-2. (L. F. B.)*

**Pneumonectomy.** The author reviews 140 cases of pneumonectomy recorded in the literature as well as his own 22 cases. Excluding all cases prior to 1931, 62 of the 140 cases were done for malignant lesions and 45 for benign lesions. Mortality in this group was 68 per cent for the malignant cases and 24 per cent for the benign. In 15 of the author's 22 cases, pneumonectomy was performed for malignant disease with a mortality of 33.3 per cent, and 7 were for benign lesions without an operative death. Clinical studies in the 64 patients led to a diagnosis of primary malignancy of the lung with histological verification before death in 59. Thoracic exploration was indicated in over half of the patients harboring pulmonary cancer, since evidence of extension of the tumor beyond the lung could not be demonstrated by clinical examination. Over half the explored cases proved to be operable. Pneumonectomy was performed on 15 patients and lobectomy on 3. This places operability of primary cancer of the lung in this series at approximately 25 per cent. —*Pneumonectomy for Malignant and Suppurative Disease of the Lung, R. H. Overholt, J. Thorac. Surg., October, 1930, 9: 17. (L. F. B.)*

**Oesophagus after Pneumonectomy.**—The position of the oesophagus was studied in 6

patients who had had previous oesophagotomy performed from six months to four years previously. The marked acquisition of the displacement of the oesophagus was observed in any patient with high oesophageal displacement toward the side of previous oesophagotomy was noted in none. No disturbance of function was noted and there were no significant oesophageal symptoms following pneumonectomy. —*Oesophagus after Pneumonectomy, H. C. Moore & J. A. Bloor, J. Thorac. Surg., December, 1932, 2: 123. (L. F. B.)*

**Bilateral Pleurhage.** Two patients with cavernous tuberculosis of both apices were successfully treated with bilateral pleurhage. —*Beide Lungenpleurhage Heilung bei Lungentuberculose, D. Hochst, Zeits. f. Tuberk., October, 1932, 11: 182. (H. C. L.)*

**Treatment of Empyema.** Most empyemata should be considered a purely medical problem. They should be completely drained as soon as diagnosed, whether acute or chronic, whether tuberculous or secondarily infected. Drainage should be continued until the pleural cavity is dry. The pneumothorax space should be maintained free and large after the empyema has been cured, if that treatment is still necessary for the pulmonary lesions. The theories once expressed by Sauerbruch and Dumarest that tuberculous empyema should not be interfered with, and that the pleural cavity should be drained only when respiratory difficulty presents itself, and then drained only enough to control intrathoracic pressures, cannot be accepted, because these theories are in direct contrast with experience gained through long practice. Purely tuberculous empyemata have been treated early with thoracocentesis, then pleural lavage with a warm 1:2000 watery solution of lysoform, followed by an injection of 10 to 20 cc. of 1 per cent solution of methylene blue. This procedure has been repeated every six to seven days until the exudate thinned down; then simple thoracocenteses were done followed by the injection of 10 cc. of the methylene blue solution. This method of treatment has usually converted the exudate from pus to clear serum in about two to two and one-half months. Isotonic solution has been preferred

product could be reproduced as to analyses and potency. It was called TPT, meaning "Tuberculin Protein Trichloroacetic Acid Precipitated," and was used in a great many investigations.

At that time, 1931-1932, the biological reactions of the TPA and TPT were investigated and the significant fact was noted that they were highly antigenic, that is, capable of eliciting precipitins, of producing typical anaphylaxis, and even of inducing typical Arthus reactions, when large amounts were repeatedly injected into normal guinea pigs or rabbits. These results were more conclusive than others previously obtained with bacillary extracts, since now there were available quantities of the purified fraction which could be made up into concentrated solutions of any desired strength.

It seemed advisable, therefore, to try to obtain a fraction with less antigenicity because of the possibility of eliciting false positive reactions due to sensitization with these highly antigenic preparations. Koch's Old Tuberculin might be a source of such material. However, since Old Tuberculin, even the modified variety made in synthetic medium instead of in glycerol broth, contains so much and so many impurities, it is not possible to make direct antigenic tests with it. For example, 1 cc. of a potent Old Tuberculin contains only about 10 mg. of the specific active material in approximately 300 mg. of organic and inorganic substance, and too much toxicity would be caused by the impurities present if one injected repeatedly 10 mg. (or 1 cc.) of the material, which is the amount used for eliciting an Arthus reaction with any protein.

A concentrated filtrate from cultures of tubercle bacilli grown on synthetic medium, essentially Old Tuberculin, except for the use of synthetic medium rather than of glycerol broth, can easily be freed of the excess salts and glycerol present by means of ultrafiltration, but even following this, about 50 per cent of the residue consisted of carbohydrate. Thus, further purification was necessary and it was found that precipitation of the ultrafiltered product with trichloroacetic acid, removal of the acid with ether and simultaneous drying with the ether yielded a potent product, stable in its potency for years, and of the same degree of purity as the TPT, but far less sensitizing. This product was called the Purified Protein Derivative Tuberculin. It did not precipitate antiserum, nor produce a typical Arthus reaction when repeatedly injected intracutaneously in large amounts. Some oedema was produced, but the induration and necrosis of the typical Arthus reaction were lacking. However, when it was adsorbed to aluminum hydroxide or charcoal, it then did become

antigenic and did stimulate the production of precipitins, resembling a haptene.

This product proved to be very satisfactory for skin testing. It was, therefore, put up in quantitative tablet form, so that the addition of a specified amount of diluent to each tablet would give a solution already diluted for use as first or second intracutaneous dose. On the basis of extensive trial the first dose was chosen as 0.00002 mg. and the second dose as 0.005 mg. The product has been used widely in tuberculin testing programs in this country and abroad.

This Purified Protein Derivative Tuberculin is practically nonantigenic and, in addition, in physico-chemical experiments it proved to be a comparatively small molecule, while the fractions made from the untreated tuberculin were larger molecules and were antigenic. Therefore, the idea was conceived that there may be a unit tuberculin protein molecule containing active groups responsible for the tuberculin activity. This unit by itself is not completely antigenic but when two or more of these units are aggregated a molecule is produced which is antigenic. The idea of a unit molecule and association of units is analogous to the conception of Professor Svedberg, concerning most proteins studied by him and his associates. He postulated the smallest protein unit molecule to be about 17,000 in molecular weight and actually all proteins studied have molecular weights which are multiples of this unit weight, including substances with weights 2, 4, 8, 16, 24, 48, 96, 192, 384 and 576 times this figure. Certain proteins, by association or dissociation, can exist as several different sizes, according to the environmental conditions.

It was decided that it would be worth while to determine whether the tuberculin protein might fit into the system expressed above. The importance of such an organization or system of molecules in understanding the nature of the tuberculin reaction cannot be overestimated. Furthermore, from the standpoint of general immunology or protein chemistry, no more ideal substance could be found for such a study since few biologically active protein molecules have shown such remarkable stability in potency.

Therefore, an extensive study was made in Professor Svedberg's laboratory on representative tuberculin protein molecules, among which were the TPA, the most antigenic, and the Purified Protein Derivative, the least antigenic molecule. Physico-chemical analyses indicated that both products were chemically heterogeneous and required further purification before accurate molecular weights could be found. When this

purification was made the antigenic molecule was found to have a molecular weight of about 32,000, and the one isolated from the Purified Protein Derivative a weight of 17,000 to 18,000. Thus, the original idea appeared to be confirmed, but other complicating factors have since appeared.

In the meanwhile, while all the Purified Protein Derivative preparations made in our own laboratory seemed to have equal potency, those made in some other laboratories proved to be weaker. The reason for this had to be determined, especially in view of the fact that there came at this time to the National Tuberculosis Association a request for the preparation of a very large quantity of Purified Protein Derivative to be used as an official standard. Furthermore, during the more illuminating studies made possible by the refined physico-chemical and analytical methods recently available, it became apparent that it might be possible to produce by a simple method, as would be necessary for large scale production, a potent preparation of much greater chemical purity than heretofore. It was possible that chemical denaturation, to which purified proteins are peculiarly liable, was a cause of the variation in potency.

It seemed probable that less denaturation would result from (1) carrying out the entire procedure in the cold room, at 4 to 5°C, (2) using less heat, that is, by not evaporating on the steam bath, (3) using a weaker acid than 10 per cent trichloroacetic acid for precipitation, and (4) obtaining the final product in dry form by the lyophile process, rather than by drying with ether or simply *in vacuo*.

Furthermore, through spectrographic, electrophoretic and analytical methods, it became evident that the original Purified Protein Derivative product contained more of the impurities, nucleic acid and polysaccharide, than one desires in a purified product. Recent studies in the Tiselius electrophoresis apparatus showed that the nucleic acid and protein readily separated and traveled as separate components at a reaction more alkaline than pH 5.0, whereas on the more acid side they migrated as a single component. Thus, if the precipitation could be made on the alkaline side rather than by acid, as was usually the case, a product with less nucleic acid should be expected.

In view of all these considerations, modifications were introduced in the original method for making the Purified Protein Derivative. The greater part of a year was utilized in the production of the large lot for an official standard, which was prepared with the collaboration of Mr. John Glenn at the Sharp and Dohme Laboratories. The proposed changes in



the method of preparation were tested in pilot experiments while the larger quantity of tuberculin was concentrating on the ultrafilters. The resulting products were analyzed and tested for potency and proved to be far more pure chemically and also twice as potent biologically as previous preparations, indicating that there was less denaturation.

Therefore, the large lot of Purified Protein Derivative was made by the modified procedure, including precipitation by half saturation with ammonium sulfate at pH 7.0, use of ice box temperature throughout the entire procedure, elimination of the evaporation on the steam bath and final drying from the frozen state. The exact details of the process can be found in the following paper. Approximately 3,500 cultures of human type tubercle bacilli were used, and a final yield of 107 g of Purified Protein Derivative was obtained.

The product is being thoroughly investigated and it is hoped that even much more can be done than has so far been done. The results to date are as follows. The dried product is almost colorless, easily soluble in water and contains only 1.2 per cent nucleic acid and 5.9 per cent polysaccharide. It is twice as potent as our previous standard, that is, 0.000,01 mg elicits as intense reactions in sensitive patients as 0.000,02 mg of the previous product.

But the study is not yet finished, for it has proved to be somewhat more antigenic in producing the Arthus reaction than our previous Purified Protein Derivative, although less so than the unheated TPA. Repeated injections with small amounts, comparable to ten times our usual second dose, however, do not lead to significant sensitization in guinea pigs. Precipitins are also found in the sera of the sensitized rabbits and these precipitins show a certain degree of specificity different from the TPA.

This is all very interesting in view of the fact that the molecular weight has proved to be only about 10,500, that is, apparently smaller than the previous Purified Protein Derivative molecule. The sedimentation and diffusion curves show some heterogeneity and the electrophoretic pattern shows the presence of two mobile components. Attempts are being made to separate these two components. It is hoped that similar studies can be made with the unheated tuberculin for comparison.

In view of the fact that this Purified Protein Derivative has so low a molecular weight and still has the ability to elicit precipitins, it is possible that the size of the molecule is not as important a factor in the antigenicity as previously thought. It would seem rather that the po-

tency may be inherent in some part of the protein molecule and the antigenicity in some other part of the same or different molecule. The masking of either group would cause a loss in the respective potency. The exact relationship between these two properties is still not entirely clear.

The problem, however, can now be considered to be markedly limited, for now we have a highly potent molecule, which is practically free of nucleic acid and polysaccharide, so that one need no longer consider the active principle to be a nucleoprotein or a mucoprotein. On the other hand, the potent protein fraction still does not fulfil all the requirements of the most exacting modern physico-chemical methods for a homogeneous molecule. There still seems to be some contamination of the specific protein molecule with other protein. Whether it is different protein or some of the same protein in different combination or denatured is still not clear. From the practical standpoint this may not be important, but from the theoretical standpoint, in broadening our understanding of the nature of the tuberculin reaction, it will be important to pursue the problem further. The goal may not be so far away, since one product has been prepared which seems to contain very little of the contaminating fraction, without recognizable change in tuberculin potency.

All of the substances mentioned are to be found in Old Tuberculin, and, when one realizes the great complexity of such a mixture, it becomes clear that it is unreasonable to expect too close correspondence in the results obtained by its use.

Recently, it has been found that certain of these highly purified fractions, as well as being more potent per unit, give a larger percentage of reactors to the second dose strength intracutaneous test than previous preparations. The same thing was true with certain preparations of Old Tuberculin. The explanation of this fact is not yet clear, but is being intensively investigated. A corresponding increase in percentage of reactors to the first dose has not been found.

Much work is in progress to locate the limit of the dosage which will detect all those individuals with clinically significant disease, and then another dose which will detect those of epidemiological significance as well. From the data on hand, it would seem that the 0.000,02 mg originally chosen for the first dose fulfils, at least within a few per cent, the former requirement. A slightly larger dose (0.0001 mg) may detect even the few additional persons. It is quite clear, however, that the

usual second dose is larger than is necessary, and perhaps need not be used for this purpose

The proper final dosage for epidemiological studies is not as yet so easily prescribed because a great many complicating factors must be considered. Questions such as a cross sensitization to organisms or substances other than the tubercle bacillus or its products, which may vary in different localities, a nonspecific irritability in certain persons and the degree of sensitization of different people, as well as personal differences in the interpretation of small reactions, must be considered. More work must be done before a clear distinction can be made between the truly specific and the nonspecific reactions to the larger dosage

# TUBERCULIN PURIFIED PROTEIN DERIVATIVE<sup>1</sup>

Preparation and Analyses of a Large Quantity for Standard

FLORENCE B. SEIBERT AND JOHN T. GLENN

The object of preparing this single large lot of Purified Protein Derivative was to secure a product of the highest degree of purity and potency and in amount sufficient for deposit as an official standard tuberculin. The method used was a modification of the original method published in 1934 (1). It includes a number of changes introduced to prevent denaturation of the specific protein responsible for the tuberculin reaction. For example, the procedures of concentration by ultrafiltration and purification were carried out entirely at low temperature, 5-6°C. The period of heating was limited to the heating in the Arnold sterilizer and there was no concentration on the steam bath. In order to secure a colorless product Long's synthetic medium was substituted for the Dorset culture medium originally used. The difference in the composition of the two media lay only in the quantity of some of the constituents, except for glucose, of which there was none in Long's medium. The reaction of the solution was kept at a pH of 7 to 7.4 throughout the entire process, and the precipitations were made at this pH. This latter modification was based upon electrophoretic studies (2), which showed that at reactions more alkaline than pH 5.0 the nucleic acid readily separated from the protein and migrated with a much greater mobility, whereas on the acid side of pH 5.0 the two substances migrated as a single substance. Some of these modifications had already been adopted by Jensen and his associates (3).

The method finally adopted was established through a number of pilot determinations, made while the tuberculin filtrate was concentrating. For example, two small aliquots, taken from the concentrating tuberculin, were precipitated by means of 2 per cent trichloroacetic acid, four or five times, as indicated in table 1. The final precipitates were put into solution, neutralized with sodium hydroxide and washed free of

<sup>1</sup>From the Henry Phipps Institute of the University of Pennsylvania, Philadelphia, and the Mulford Biological Laboratories, Sharp and Dohme, Glenolden, Pennsylvania

sodium trichloracetate on the ultrafilter, filtered through the Seitz pad and analyzed They were designated as IIIa and IIIb in the table

TABLE 1

*Analyses*

PURIFIED PROTEIN DERIVATIVE PREPARATION	TOTAL VOLUME OF SOLUTION USED	NUMBER OF TIMES PRECIPITATED	PROTEIN	NUCLEIC ACID	POLYSACCHARIDE
	cc		per cent	per cent	per cent
IIIa	75	5	46.9	25.2	27.9
IIIb	20	4	49.2	27.2	23.6
IIIa2	35	3	93.7	0.8	5.6
49609	4,175	5	96.0	1.7	2.9
Standard	11,900	8	92.9	1.2	5.9

TABLE 2

*Skin tests on pilot lots in dispensary clinic patients*

PREPARATION OF PURIFIED PROTEIN DERIVATIVE	FIRST DOSE				SECOND DOSE			
	Dose	Number Tested	Number Positive	Average Dimensions of Reaction	Dose	Number Tested	Number Positive	Average Dimensions of Reactions
20b	mg			mm	mg			mm
(Original Standard)	0.000,02	157	62	16.4 x 15.4 x 2.0	0.005	84	42	20.4 x 17.9 x 2.1
71-2	0.000,01	157	62	17.1 x 16.0 x 1.9	0.0025	84	42	20.5 x 18.5 x 2.1
(Present Standard)								
71-2	0.000,01	41	25	16.7 x 14.8 x 1.9	0.0025	13	10	18.6 x 16.6 x 2.3
IIIa2†	0.000,01	41	25	17.5 x 16.1 x 1.9	0.0025	13	10	19.0 x 18.0 x 2.3
71-2	0.000,01	8	7	15.4 x 13.8 x 1.9				
IIIb*	0.000,01	8	7	18.2 x 17.4 x 1.9				
71-2	0.000,01	79	59	17.1 x 15.7 x 1.9	0.0025	17	13	16.5 x 14.4 x 1.9
49609†	0.000,01	79	59	16.8 x 16.1 x 1.9	0.0025	17	13	16.8 x 15.9 x 1.9

\* Preparation by precipitation with 2 per cent trichloroacetic acid

† Preparation by precipitation with neutral ammonium sulfate

A third aliquot was precipitated three times by the addition of an equal volume of saturated ammonium sulfate, previously neutralized. The final precipitate was redissolved, washed free of ammonium sulfate, filtered through the Seitz filter and analyzed. It was designated as IIIa2 (table 1).

Another pilot experiment consisted of the production of 41 g of Purified Protein Derivative by the method described for IIIa2, except that the tubercle bacilli were grown upon the Dorset synthetic medium. This preparation was designated as 49609 (table 1)

The analyses on these pilot lots showed that the products made by trichloroacetic acid precipitation (IIIa and IIIb) contained a very high percentage of nucleic acid and polysaccharide, whereas those preparations made by neutral ammonium sulfate precipitation contained almost negligible traces of nucleic acid and very low amounts of polysaccharide. In fact, they were so pure that a standardization of the final solutions on the basis of their nitrogen content was justified.

The potency of the pilot lots proved to be excellent and in both cases equal to that of a product (71-2) used as a standard. This latter product was twice as potent as the previous standard (20b) prepared by the original method (see table 2).

On the basis of these results it was decided to use the method employed in making the IIIa pilot lot, for the preparation of the large standard lot, to be designated standard Purified Protein Derivative. The procedure was as follows:

#### PREPARATION OF THE STANDARD PURIFIED PROTEIN DERIVATIVE

The human type of tubercle bacillus, strain DT, obtained from the laboratories of the Bureau of Animal Industry, Washington, was seeded on veal infusion broth and when sufficiently grown, planted on Long's synthetic medium<sup>2</sup> in one litre bottles, containing about 200 cc each. From 498 to 898 bottles of medium were planted at a time on six different occasions between June and September, 1939, as shown in table 3. In all there were 3,664 cultures and 733 litres of original medium. After incubation at 37.5°C for from eight to ten weeks, the cultures were shaken and heated in the Arnold sterilizer for three hours. They were then taken into a large cold room where the temperature was maintained constantly at 4° to 5°C, and all subsequent manipulations were made

<sup>2</sup> Asparagine	5 g
Ammonium citrate	5
Potassium acid phosphate	3
Sodium carbonate (anhydrous)	3
Sodium chloride	2
Magnesium sulfate	1
Ferric ammonium citrate	0.05
Glycerol	50
Water to	1000

at this temperature. The bacilli were filtered from the culture liquid, first through a Buchner funnel and then through a Mandler candle. The total volume of filtrate was 530 litres.

It was believed originally that no preservative would be needed during the ultrafiltration at this low temperature, but it was soon found on the pilot lots that certain bacteria grew luxuriantly and that 2 cc of toluol per litre were required to prevent their growth. Consequently three parts of tuberculin filtrate were mixed with one part phosphate buffer<sup>3</sup> at pH 7.3, containing 8 cc toluol per litre, and this then was ultrafiltered. During the ultrafiltration, buffer containing 2 cc toluol per litre was continuously added and in this way a concentration of 2 cc toluol per litre was maintained constantly.

TABLE 3  
*Preparation of the Standard Purified Protein Derivative*

LOT NUMBER	VOLUME OF ORIGINAL MEDIUM	VOLUME OF FINAL FILTRATE	FINAL VOLUME OF CONCENTRATED FILTRATE	TOTAL YIELD IN G (BASED ON 2 PER CENT TRICHLORACETIC PRECIPITATION)	TOTAL GRAMS ISOLATED
	<i>litres</i>	<i>litres</i>	<i>cc</i>		
1	112.6	86.8	1,200	16.2	
2	111.2	73.3	3,000	21.2	
3	99.6	68.8	1,000	9.8	
4	99.6	72.6	1,000	11.3	
5	175.6	130.4	3,700	40.0	
6	134.2	98.1	2,000	19.5	
Total	732.8	529.9	11,900	118.0	107

As in the original method, the filtered tuberculin was concentrated by means of ultrafiltration (1) on alundum shells impregnated with 11 per cent gun cotton, about 50 such filters being in use for each lot of filtrate. About 50 litres of the buffer were also added to each lot during the ultrafiltration, in order to wash out the medium constituents, and the concentration was continued until the solution contained about 0.7 to 1.3 per cent protein. This was easily determined by the precipitation test (4) with 2 per cent trichloroacetic acid. A total of 11.9 litres of concentrated solution were obtained from the entire filtrate.

<sup>3</sup> The buffer was made as follows: 9.078 g of  $\text{KH}_2\text{PO}_4$  were dissolved in 1000 cc distilled water, 23.87 g of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  were dissolved in 1000 cc distilled water. Two parts of the solution of the potassium salt were mixed with eight of the sodium salt, and the mixture was then diluted 1 to 5 with distilled water.

Each lot of concentrated filtrate was then filtered through a Mandler candle and lyophilized, in order to maintain it in sterile and stable form until all of the other lots were ready. The dried residues were almost white and very fluffy in appearance.

The lyophilized residues were finally redissolved in 4 litres of buffer and complete solution was obtained except for a slight turbidity, due probably to a small amount of denatured protein. This solution was distributed in twenty 400 cc centrifuge bottles, 200 cc to a bottle. To each was added 200 cc saturated ammonium sulfate, previously neutralized to phenol red with solid disodium phosphate. The resultant ammonium sulfate precipitates were centrifuged, the supernatant solutions syphoned off and the precipitates dissolved in buffer. It was necessary, at this point, to redistribute the precipitate in 30 bottles (total 6 litres) instead of 20 bottles, in order to effect complete solution.

The clear solutions were again precipitated by half saturation with neutral ammonium sulfate, centrifuged and redissolved, and this was repeated six more times, making a total of eight precipitations. One bottle broke after the fifth precipitation and this was worked up separately. The seventh and eighth supernatants were colorless and water clear, and presumably as free as possible, as a result of the repeated precipitations, from the nucleic acid and polysaccharide. The final solution had somewhat more turbidity than existed at the beginning of the precipitations, probably due to denatured protein. It was filtered with difficulty through the Mandler filter, but the resulting solution was entirely clear, of a deep amber color, and had an opalescence such as is seen in strong protein solutions. The volume was 9,300 cc, and the 2 per cent trichloroacetic acid test indicated that it contained about 113 g of protein.

The solution was then ultrafiltered and washed free of sulfate with 67.3 litres buffer containing 2 cc toluol per litre. The ultrafiltrate was practically colorless from the beginning and showed a trace of precipitate with 10 per cent trichloroacetic acid only after the test solution stood for twenty-four hours, a result indicating very little loss of the protein. The concentrated solution was filtered through paper and the volume was 7,250 cc. It was then filtered through the Mandler candle and with the wash the final volume was about 7,850 cc.

A nitrogen determination on this sterile solution showed it to contain 13.3 mg protein per cc, based on 16.3 per cent nitrogen for the protein (5). Thus there was a total yield of 104.4 g Purified Protein Derivative.



The precipitate in the bottle which had broken in the centrifuge was purified separately in a similar manner and yielded 3.87 g Purified Protein Derivative

Vials were then filled with 3.75 cc, equivalent to 50 mg Purified Protein Derivative, or 0.75 cc, equivalent to 10 mg. The product was dried by quick freezing of the sterile solutions and drying in the frozen state, that is, by the lyophile process. This method has been shown (6) to preserve the potency quantitatively, even in high dilutions such as are used for diagnostic testing. There was some loss in the filling of the vials and thus the final yield was 107 g Purified Protein Derivative

As noted in the description of the method used for preparing the Purified Protein Derivative, it was necessary to use toluol in order to prevent contamination of the tuberculin during concentration, even

TABLE 4  
*Skin tests in dispensary patients*

PURIFIED PRO- TEIN DERIVATIVE PREPARATION	0.00001 MG			0.0025 MG.		
	Number Tested	Number Positive	Average Dimensions of Reaction	Number Tested	Number Positive	Average Dimensions of Reaction
			mm			mm
71-2 Standard	106	82	20.6 x 17.3 x 2.1	24	14	29.9 x 24.5 x 2.4
	106	82	20.7 x 20.1 x 2.2	24	14	30.8 x 26.4 x 2.5
	0.00002 MG			0.005 MG		
81 Standard	97	75	23.7 x 22.6 x 2.5	23	19	21.1 x 21.1 x 2.4
	97	75	23.1 x 21.1 x 2.4	23	19	20.4 x 18.3 x 2.4

though the procedure was carried out at 4 to 5°C. This necessitated great vigilance and repeated filtrations through the Mandler candle and thus added greatly to the labor involved. Therefore, a small lot of Purified Protein Derivative was prepared, in which every step in the preparation was identical with that used in the case of the Standard Purified Protein Derivative, except phenol was used as a preservative. After the culture was freed of bacilli by filtration through the Mandler candle, to every litre of filtrate was added 250 cc of a phosphate buffer solution of  $\mu$  0.1 and containing 2.5 per cent phenol. This resulted in a final buffer concentration of  $\mu$  0.02, pH 7.3 and 0.5 per cent phenol with the tuberculin. Thus the concentration by ultrafiltration could be carried out more leisurely and with no danger of contamination. The final washing on the ultrafilters to remove ammonium sulfate was also

made in the presence of 0.5 per cent phenol. The final product (8) contained 0.35 per cent nucleic acid and 3.6 per cent polysaccharide, and proved to be equal in potency to the Standard Purified Protein Derivative, as seen in table 4. Therefore, it is safe and even advisable to use 0.5 per cent phenol as a preservative during the preparation of Purified Protein Derivative.

#### CHEMICAL AND PHYSICO-CHEMICAL TESTS ON THE STANDARD PURIFIED PROTEIN DERIVATIVE AND PREPARATION 49609<sup>4</sup>

Analyses for nucleic acid by means of the diphenylamine reaction showed 1.2 per cent nucleic acid, and for polysaccharide by means of the

TABLE 5  
*Physico-chemical properties*

PURIFIED PROTEIN DERIVATIVE PREPARATION	S <sub>20</sub>	D <sub>20</sub>	MOLECULAR WEIGHT	MOBILITY $\times 10^3$ CM <sup>2</sup> VOLT <sup>-1</sup> SEC <sup>-1</sup>			
				$\mu = 0.1$		$\mu = 0.02$	
				Ascending	Descending	Ascending	Descending
				At pH 7.3			
Standard	0.76	8.80	8,200	-7.5, -4.3	-6.2, -3.7	-12.9, -9.6	-6.7, -2.6
	1.15		12,400				
	1.013		10,900				
49609	1.32	8.65	14,500	-7.6	-6.2	-12.9	-7.2, -2.97
Standard				At pH 8.0			
				-8.1, -4.5	-7.1, -3.0	-12.2, -9.9	-8.0, -2.5

carbazole test showed 5.9 per cent total polysaccharide (see table 1). This latter figure includes 4.7 per cent true tuberculin polysaccharide.

The results of physico-chemical studies are shown in table 5. The determinations of the sedimentation and diffusion constants were made by Dr. Janet McCarter and Mr. Dennis Watson with the use of the Svedberg ultracentrifuge and the Lamm diffusion cell, in the laboratory of Dr. J. W. Williams at the University of Wisconsin, to all of whom we express our appreciation. An average of the molecular weights, calculated from three determinations of  $S_{20}$ , gave 10,500. Thus the average molecular weight is smaller than the 15,000 to 18,000 found for the

<sup>4</sup> Work on the further purification of these fractions is in progress in collaboration with the laboratory of Professor Arne Tiselius, Uppsala, Sweden.

Purified Protein Derivative preparations made by the original method and studied previously (5). The sedimentation curves showed some heterogeneity. The corresponding curves for the Purified Protein Derivative 49609, which proved to have a molecular weight of about 14,500, were more homogeneous. Both curves, however, showed more homogeneity than did a Purified Protein Derivative made by the original method (see figure 1). The diffusion curves of the preparation 49609 almost coincided with the normal distribution curve, indicating a high

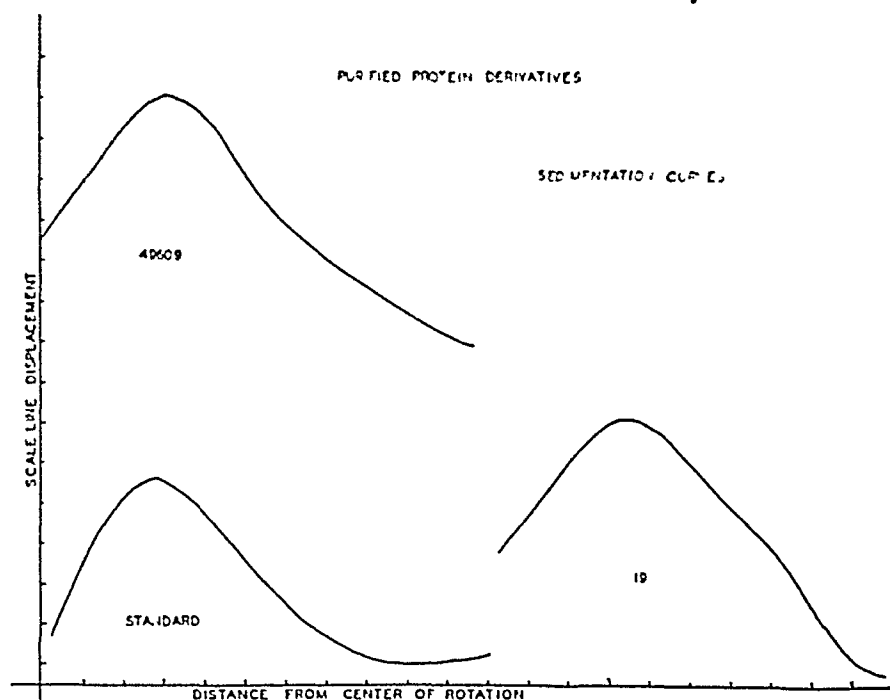


FIG 1

degree of homogeneity, but this was not true for the curves of the Standard Purified Protein Derivative.

The electrophoretic mobilities, as determined in the Tiselius electrophoresis apparatus (7), were considerably different at the ascending boundaries in the two different buffer concentrations of  $\mu = 0.1$  and  $\mu = 0.02$ , whereas at the descending boundaries they were more nearly alike (see table 5). Furthermore, identical mobilities were found for the fast components in the Standard Purified Protein Derivative and in the

49609

# ELECTROPHORETIC CURVES OF PURIFIED PROTEIN DERIVATIVES

STANDARD



A

$\mu = 0.02$



D



A



D



A

$\mu = 0.1$



D



A

$\mu = 0.2$



D

Electrophoretic curves of  
purified protein derivatives

Purified Protein Derivative 49609 indicating that a similar component exists in the two preparations. Figure 2 shows the electrophoretic patterns obtained. It is clear that in both preparations sharper curves on the ascending side (A) were obtained in the buffer of lower concentration,  $\mu = 0.02$ . The curves on the left hand side of the ascending diagrams represent polysaccharide plus some anomalous ( $\delta$ ) boundary and those on the right are the migrating protein boundaries. In the case of the Standard Purified Protein Derivative, especially at  $\mu = 0.1$ , two mobile components appear, which do not separate into distinct boundaries, but appear to cling together, making the boundary broad and diffuse. Evidence of this tendency for the boundary to spread is also seen in the broad curve (A) for the mobile component in Purified Protein Derivative 49609 at  $\mu = 0.1$ . That there are two mobile components in Purified Protein Derivative 49609, in addition to the immobile one, is seen in the descending pattern, at  $\mu = 0.02$ , which is very diffuse.

All descending boundaries (D) spread out practically through two compartments. The mobility of the slower component is of the order found for the slower components associated as impurities with one type of polysaccharide isolated from the tuberculin filtrate (8). In the case of this polysaccharide there was evidence of a phenomenon of great tenacity between it and the nitrogenous impurities, some of which were protein, and it is possible that some of this same effect may be present in the case of the Standard Purified Protein Derivative. If such is the case, it would explain why 5.9 per cent polysaccharide was still present after eight precipitations and also why the electrophoretic curves appear to be so diffuse in spite of the fact that the product by analyses is purer than all previous preparations of Purified Protein Derivative. The product will be studied more extensively from this standpoint in the future.

The presence of a greater amount of this component with low mobility in the Standard Purified Protein Derivative than in the preparation 49609, as is evident from the electrophoretic diagrams, might also explain the fact that the sedimentation curves of the former preparation are less homogeneous. It is certain that more of the slow component is evident at the higher salt concentration,  $\mu = 0.1$ . Pedersen (9), and recently Longworth, Cannan and MacInnes (10) have stated that there is greater association between components at low salt concentration, especially if one is carbohydrate.

BIOLOGICAL TESTS ON THE STANDARD PURIFIED PROTEIN DERIVATIVE AND  
PURIFIED PROTEIN DERIVATIVE 49609

Lethal tests in tuberculous guinea pigs showed that 2 out of 6 died in twenty-four hours following an intraperitoneal injection of 0.5 mg of the Standard Purified Protein Derivative, and one out of 3 died following an injection of 1.0 mg. Autopsy revealed typical tuberculin death with congestion of the splanchnic area, including the adrenals, and fluid and mucus in the abdominal cavity.

Intracutaneous skin tests in human beings (table 4) indicated that the Standard Purified Protein Derivative gave reactions of equivalent size to the 71-2 preparation and was, therefore, twice as potent as the previous standard (see table 2 also).

A study was then made to determine how much sensitization could be brought about by repeated intracutaneous injections of large amounts (10 mg) of the Standard Purified Protein Derivative.<sup>5</sup> It had been noted previously (11) that the Purified Protein Derivative gave comparatively smaller skin reactions following repeated injections than did the tuberculin protein fractions isolated from unheated filtrate and that these reactions lacked the induration and necrosis characteristic of the typical Arthus reaction elicited by the latter. Since the actual reactions obtained in this series had not been recorded previously they are noted in table 6. Comparisons, therefore, can be made with table 7, which records the reactions obtained by repeated injections of the Standard Purified Protein Derivative. It is clear that more sensitization occurred with the Standard Purified Protein Derivative than with the previous Purified Protein Derivative, but not as much as with the protein precipitated by ammonium sulphate (TPA) from unheated filtrate.

An effort was, therefore, made to determine whether significant sensitization might occur from repeated intracutaneous tests with small doses of the Standard Purified Protein Derivative more nearly like the usual second dose in man. Ten times the usual second dose, or 0.05 mg, was used and table 8 shows that nine such injections in normal guinea pigs did not produce reactions of any significance. In view of the small reactions that did occur, as well as other recent studies suggesting a nonspecific nature of the second dose reactions, it is probable that very small and questionable reactions to the usual second dose should be discounted.

<sup>5</sup> This series of tests was made by Mr. Dennis Watson.

TABLE 6

FRACTION	10 MG INJECTED ON	RABBIT #227	Dimensions of reaction at twenty four hours in mm		RABBIT #2033
TPA (from unheated filtrate)	4/26	22 x 32 (pale, slight oedema)	37 x 50 (slight oedema)	40 x 15 (erythema, slight oedema)	
	4/30	30 x 42 (light red, oedema)	40 x 42 (more oedema) (10 x 10 centre)	35 x 36 (oedema) (5 x 5 centre)	
	5/3	48 x 50 (much oedema)	65 x 90 (much oedema)	25 x 60 (pale oedema)	
	5/8	85 x 120 (much oedema)	112 x 125 (induration) (8 x 10 centre)	37 x 65 (oedema)	
	5/11	80 x 90 (some induration) (7 x 7 centre)	60 x 90 (marked induration) (7 x 11 centre)	70 x 80 (some induration) (10 x 12 necrosis)	
	5/21	95 x 100 (marked induration) (7 x 10 centre)	65 x 80 (marked induration) (9 x 9 necrosis)	80 x 110 (marked induration) (8 x 10 centre)	
	6/1	73 x 88 (marked induration)	85 x 95 (marked induration) (15 x 15 centre)		
	6/4	95 x 110 (pale, some induration)	55 x 62 (some induration) (10 x 12 necrosis)	50 x 80 (marked induration)	
Reaction to 10 mg Purified Protein Derivative at end of series of injections					
Purified Protein Derivative	4/30—1st				
	6/1 —7th				
Purified Protein Derivative adsorbed to Al(OH) <sub>3</sub>	4/30—1st				
	6/1 —7th				

Another method for studying sensitization, that is, by means of the precipitin reaction, was also investigated. The 2 normal rabbits which had received the series of eleven intracutaneous injections of 10 mg of the Standard Purified Protein Derivative were bled to death. Table 9 shows that their sera contained precipitins to the three antigens tested. This is contrary to results obtained previously (11) in which Purified Protein Derivative did not elicit precipitins of any significance. Some of these previous results are included in the table for comparison. However, when in the earlier studies Purified Protein Derivative had been

TABLE 7  
*Sensitization by repeated intracutaneous injections*

STANDARD PURIFIED PROTEIN DERIVATIVE 10 MG. INJECTED ON	DIMENSIONS OF REACTION IN RABBIT #659 IN MM	DIMENSIONS OF REACTION IN RABBIT #511 IN MM
7/5	0 (slight erythema)	20 x 30 (erythema and oedema)
7/8	48 x 50 (some induration)	40 x 83 (erythema and oedema)
7/11	40 x 60 (erythema and oedema)	38 x 55 (induration)
7/15	50 x 70 (marked induration)	60 x 70 (induration)
7/19	50 x 60 (marked induration)	50 x 80 (induration)
7/22	50 x 50 (erythema and induration) (5 x 5 centre)	50 x 60 (induration)
7/23	50 x 50 (induration) (10 x 10 centre)	50 x 50 (induration) (5 x 5 necrosis)
8/2	40 x 50 (induration) (5 x 5 centre)	40 x 50 (induration) (5 x 5 centre)
8/12	40 x 40 (induration)	40 x 55 (induration)
8/19	40 x 50 (induration) (5 x 5 centre)	30 x 40 (induration)
8/26	40 x 50 (induration)	40 x 40 (induration)

adsorbed to aluminum hydroxide or charcoal and then injected, precipitins were obtained. It is to be noted that in these latter cases, as well as in the case of the antisera to the Standard Purified Protein Derivative, the highest titres were obtained with the homologous antigens. Likewise the highest titres to the TPA antisera were obtained with the TPA. Thus, there appears to be some specificity in the two molecules. The fact that the Standard Purified Protein Derivative is a much purer preparation than the previous Purified Protein Derivative as determined by chemical analyses, and that it is no larger in molecular weight but, in fact, even slightly smaller, suggests that the specificity observed may be due to the fact that certain groups are unmasked in the Standard Purified Protein Derivative or that there is less denaturation than in the



TABLE 8  
*Reactions to repeated intracutaneous tests of 0.05 mg. Standard Purified Protein Derivative—dimensions in mm*

NORMAL GUI TEA FIG	TIME OF READ ING	10/15 0.005 MG	10/22	11/4	11/7	11/11	11/14	11/18	12/1	12/9
	hours									
1	24 48	0 0	0 0	trace 0	10 x 10 x 1 ?	7 x 5 x trace 0	7 x 8 x trace trace	1 x 1 x trace 0	trace 0	0 0
2	24 48	0 0	0 0	0 0	0 0	4 x 5 x trace 0	5 x 5 x trace 0	0 0	7 x 8 x 1 0	0 0
3	24 48	0 0	6 x 7 x trace 0	6 x 9 x trace 0	8 x 9 x trace 0	12 x 13 x 1 10 x 12 x 1	1 x 5 x trace trace	8 x 9 x 1 1 x 4 x trace	4 x 4 x trace trace	8 x 9 x 1 0
4	24 48	0 0	5 x 6 x trace 0	0 0	12 x 12 x 1 0	12 x 12 x 1 4 x 5 x trace	6 x 8 x 1 4 x 5 x trace	7 x 8 x 1 trace	6 x 8 x 1 0	7 x 8 x 1 0
5	24 48	0 0	? (scratch) ?	8 x 9 x trace 0	7 x 10 x 1? (scratch) 4 x 5 x trace	7 x 9 x 1 4 x 6 x 1	0 0	9 x 10 x 1 3 x 4 x trace	9 x 10 x 1 0	9 x 9 x 1 0
6	24 48	0 0	0 0	8 x 10 x trace 7 x 8 x trace	10 x 12 x 1 10 x 11 x trace	6 x 8 x 1 5 x 8 x trace	1 x 5 x trace 0	8 x 8 x 1 0	0 0	0 0

case of the previous Purified Protein Derivative. The greater potency of the Standard Purified Protein Derivative would, furthermore, support these suggestions.

The first possibility, that is, that certain reactive groups may be unmasked in the more highly purified product, was tested in the following manner. The impurities, namely, nucleic acid and the two types of polysaccharide mentioned above (8) which had been removed, may be suspected to be the substances capable of causing the masking effect.

TABLE 9  
*Precipitin titres*

ANTISERA	ANTIGENS				
	Purified Protein Derivative 20	Standard Purified Protein Derivative	Purified Protein Derivative 49609	TPA	Polysaccharide (Tuberculin)
To Purified Protein Derivative 20	1 400 0			1 200 0	
To Purified Protein Derivative adsorbed to $Al(OH)_3$	1 400,000			1 40,000	
	1 400,000			1 100,000	
To Purified Protein Derivative 20 adsorbed to charcoal	1 400,000			1 400,000	
To Standard Purified Protein Derivative	1 10,000	1 70,000	1 100,000	1 30,000	
		1 100,000	1 100,000	1 20,000	
To TPA	0			1 100,000	
	1 1,000-4,000			1 400,000	
	1 10,000			1 400,000	
	0	1 2,000	1 2,000	1 100,000	
To Whole Dead Tubercle Bacilli (Horse Antiserum #5807A)	1 100,000	1 40,000	1 40,000	1 70,000	1 15,000,000

Therefore, each of them, in highly purified form, was added to Purified Protein Derivative and then the precipitin tests were made, using these mixtures as antigens against one of the Standard Purified Protein Derivative antisera. No effect was noted on the precipitin titre in any case.

#### SUMMARY

A large quantity of Purified Protein Derivative Tuberculin was prepared to serve as a tuberculin standard.

Modifications in the original method of preparation were introduced, which yielded a product with much reduced amounts of nucleic acid (1.2 per cent) and polysaccharide (5.9 per cent) and a potency, as determined by the Mantoux test, twice that of the former Purified Protein Derivative. This product was made without the use of phenol, but it was shown that the use of 0.5 per cent during the preparation does not decrease the potency.

The final product was dried from the frozen state (lyophilized) and preserved in sterile form and *in vacuo*, which should insure its stability for an indefinite period of time.

Physico-chemical studies indicated that it had a molecular weight of about 10,500. The sedimentation curves showed some heterogeneity and electrophoretic diagrams also showed the presence of at least two mobile components, especially at the higher buffer concentration. Either the interaction between these components was increased at low buffer salt concentration or the formation of a second component was facilitated by increased salt concentration.

By repeated intracutaneous injections of large (10 mg.) amounts of the Standard Purified Protein Derivative into normal rabbits a certain degree of sensitization (Arthus reaction) was produced which was somewhat greater than that caused by the previous Purified Protein Derivative preparations and less than that caused by tuberculin protein precipitated with ammonium sulphate (TPA). However, repeated injections of small amounts of the Standard Purified Protein Derivative, namely, ten times the regular second dose used in the skin test, did not lead to significant sensitization in guinea pigs.

The sera of the rabbits sensitized to the Standard Purified Protein Derivative contained precipitins. There seemed to be a certain degree of specificity between the TPA and Purified Protein Derivative molecules.

We express our thanks to Dr. John Reichel for his encouragement, support and active interest throughout this work.

We express our appreciation also to Dr. O. Bird for assistance in the final precipitation of the products, to Mr. N. Harrington for his faithful attention to the lyophilizing of the fractions at various stages in the process, to Mr. J. W. Nelson for valuable assistance in the final purification and testing of the preparations, and to Miss E. DuFour for making the Mantoux tests in dispensary patients.

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# PULMONARY INSUFFICIENCY<sup>1,2</sup>

## I Discussion of a Physiological Classification and Presentation of Clinical Tests

ANDRE COURNAND AND DICKINSON W RICHARDS, JR.

Pulmonary insufficiency has been analyzed, from the point of view of pathological physiology, in several excellent recent papers. Those by Knipping (1, 2, 3) and Anthony (4, 5) are perhaps outstanding. These investigators have gone into considerable detail in their descriptions of pulmonary insufficiency, with classification and division into a number of different forms.

For the purposes of clinical medicine, it has seemed to us that the simplest possible classification would probably be the most useful, and we believe that, in the existing state of knowledge, a simple and useful classification of pulmonary insufficiency can be made.

Pulmonary function can be divided broadly into two parts: *ventilatory*, the function concerned with movement of atmospheric air into and out of the lungs, and *respiratory*, the function concerned with (a) the diffusion of oxygen from alveolar spaces into the blood, providing adequate oxygenation of haemoglobin, and (b) the elimination of carbon dioxide from blood to alveolar air.

Thus the ventilatory aspect of pulmonary function is largely mechanical. The major symptom of ventilatory insufficiency is *dyspnoea*.

The respiratory aspect of pulmonary function is largely physicochemical. The major symptoms of respiratory insufficiency are those of anoxia, of which *cyanosis* is the most obvious.

### PULMONARY INSUFFICIENCY

FORM	TYPE OF FUNCTION	SYMPTOMS
Ventilatory	Mechanical	Dyspnoea
Respiratory	Physicochemical	Anoxia (cyanosis, etc.)

It should be emphasized that the purpose of the above description is to provide a useful approach to the symptomatology of pulmonary (and

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<sup>2</sup> Under a grant from the Commonwealth Fund.

pulmonocirculatory) disease. It is not intended as an adequate analysis of all the complicated interrelations of pulmonary physiology. It is obvious, for example, that the ventilatory and respiratory mechanisms are at all times closely interrelated. Ventilatory insufficiency, if sufficiently severe, will necessarily induce respiratory insufficiency, conversely, respiratory insufficiency will add to the stimulus of the respiratory centre and tend to increase ventilation.

Of particular importance is the place where the ventilatory and respiratory functions meet, namely the alveoli. Adequate pulmonary function demands not only the inhalation of proper volumes of air, but the distribution of this air to alveolar spaces that are being perfused with pulmonary blood, in other words, the *aeration* of the ultimate alveolocapillary units. This phase we have included as a part of respiratory function.

Clinically, it is not uncommon to find cases of almost pure ventilatory insufficiency. Cases of purely respiratory insufficiency are also seen, but are rare. For the most part, however, this classification of pulmonary insufficiency will be found useful in evaluating the disability of each patient. Thus, most patients with physical disability due to chronic pulmonary disease will have some degree of ventilatory failure and also some degree of respiratory failure. A proper estimate of these two aspects may mean much in determining adequate therapy.

A still further complicating factor is cardiocirculatory failure. This also requires evaluation, as a part of the total dysfunction in any given case. As is well known, cardiac failure may manifest itself by strictly pulmonary symptoms, and pulmonary function itself may be badly compromised from purely circulatory causes.

Thus for practical purposes, four major categories of pulmonary insufficiency can be recognized:

- I Ventilatory insufficiency, or failure of the breathing mechanics to provide the required pulmonary ventilation without dyspnoea
- II Respiratory insufficiency, or failure to maintain normal respiratory gas interchange between the alveoli and the pulmonary capillaries
- III Combined ventilo-respiratory insufficiency
- IV Combined cardio-pulmonary insufficiency of various types

The object of this paper is to review the physiological principles which form the basis of this differentiation, to present a group of clinical tests used for the evaluation of pulmonary and circulatory function, and to

discuss some points of technique. In papers to follow, an attempt is made to estimate the effects on pulmono-circulatory function of various types of collapse therapy.

#### VENTILATORY INSUFFICIENCY

Ventilatory insufficiency results from decrease in *maximum breathing capacity*, increase in *breathing requirement*, or a combination of both.

##### A *Maximum Breathing Capacity*

Maximum breathing capacity, often referred to as maximum ventilatory volume (6) (*Atmngrenzwert* of the German authors), measures the maximum volume of air that can be ventilated in unit time. Maximum breathing capacity expressed in liters per minute provides, we believe, a measurement better correlated with actual ventilatory function than the measurement of the maximum volume change of a single breath without regard to time (that is, the vital capacity). Decrease in maximum breathing capacity is brought about by restriction of, or obstruction to, air circulation. Maintenance of a large maximum breathing capacity is dependent upon the integrity of the following structures:

- 1 The chest bellows, the amplitude and speed of volume change of which is regulated by a highly integrated and coordinated neuromuscular system
- 2 The tracheobronchial pulmonary airway
- 3 The pulmonary tissue, considered here chiefly for its elastic properties

Thus, limitation in maximum breathing capacity may occur (1) from abnormality of the chest wall or disturbance of the neuromuscular apparatus of breathing, as in advanced kyphoscoliosis or following diaphragmatic paralysis, or (2) from obstruction in the air passages, such as in asthma and obstructive emphysema, or (3) from limitation in pulmonary elasticity, such as in fibrosis or pulmonary congestion.

Four methods for estimating the maximum volume of air which can be ventilated per unit time have been described. Definitely contraindicated in our group of patients were methods requiring heavy exercise (7) or carbon dioxide rebreathing (8). The measurement of a *single* deep and rapid breath in relation to time, used by Gaubatz on a large scale in tuberculous patients (9), gives obviously too low values. The best method available for our purposes is that described originally by Hermannsen, which we have discussed recently (10). This consists essentially in having the subject (connected to a spirometer) perform his maximum ventilatory effort, allowing him to choose

his own rate and depth, and having this maximum ventilatory volume recorded graphically on a moving drum

To determine the maximum breathing capacity by the voluntary method of Hermannsen is simple, it does not require prolonged effort nor special training, its results are reproducible. In normal subjects the values obtained are much larger than by measuring ventilation during heavy exercise, which in the largest series reported (7) averaged 80 liters in males and 50 liters in females. In the group of 20 normal males and 20 normal females tested by Hermannsen's method, which we previously reported (10), the mean values for maximum breathing capacity were respectively 154 liters per minute for males and 100 liters per minute for females. Although based on determinations in groups of limited numbers, these values, as further studies actually in progress indicate, seem to be quite representative. A much larger series and a less uniform population with regard to age, physical characteristics and state of training, will be required before one is permitted to calculate percentage ratio of normal in pathological cases. The relation between vital capacity and maximum ventilatory volume per minute has been emphasized by Peabody. If a high correlation exists, the simple measurement of the vital capacity should permit a prediction of the maximum breathing capacity. In our two groups of normal subjects, the coefficients of correlation were  $r = +.489$  S.E.  $\pm .17$  in males ( $P$  between .05 and .02), and  $r = +.539$  S.E.  $\pm .16$  in females ( $P$  between .02 and .01), although statistically significant,<sup>3</sup> they do not approach perfection sufficiently to permit such a prediction. That is, the vital capacity cannot be relied upon as a quantitative measure of ventilatory capacity.

### B Breathing Requirement

Breathing requirement is the actual volume of ventilation per minute in any given physical state. This volume, regulated by reflex stimula-

<sup>3</sup> The value assigned to  $P$  indicates the probability that the difference observed between two means, or the correlation between two measurements, is due merely to chance. The lower the value of  $P$ , the greater the significance of a difference or of a correlation. (a) To test the significance of a coefficient of correlation ( $r$ ) in a small sample, table Va on page 174 of *Statistical Methods for Research Workers* by R. A. Fisher was used. (b) To test the significance of a difference between the means of two groups, the following calculation is made

$$t = \frac{\text{difference of the 2 means}}{\text{standard error of the difference of means}}$$
  $P$  is then read from the  $t$  value entered in the table prepared by "Student" for small samples (table, page 137 of *Statistical Methods for Research Workers* by R. A. Fisher)



tion of the respiratory centre, varies with the state of metabolism, posture, exertion, anoxia of blood and tissues, emotional and other nervous states

In the group of cases which we are reporting, it was measured (a) with the subject supine under basal conditions, (b) during a standard exercise, consisting of stepping up and down a step 20 cm high 30 times in one minute, and (c) during the period of recovery, limited to the five minutes following the cessation of exercise. This simple type of exercise is usually managed without undue fatigue, even by patients with considerable disability.

Quantitative measurements of ventilation in the three states of rest, exercise, and recovery, are secured by collecting expired air in a Tissot gasometer and

TABLE 1

*Ventilation and respiratory gas exchange in a control group at rest under basal conditions and during standard exercise\**

	REST		EXERCISE	
	Mean	Standard deviation	Mean	Standard deviation
Ventilation, lit./min. per sq. m B.S.†	3.20	± 0.65	9.70	± 1.81
Carbon dioxide output				
cc./min. per sq. m B.S.‡	101.9	± 15.0	318.1	± 73.3
cc./lit. ventilation	36.3	± 5.8	37.2	± 3.3
Oxygen intake				
cc./min. per sq. m B.S.‡	132.0	± 12.8	468.0	± 73.7
cc./lit. ventilation	16.8	± 7.1	54.8	± 6.2
R.Q.	776		678	

\* The control group consisted of 15 hospital patients without pulmonary or cardiovascular disease.

† Saturated gas at 37°C and prevailing barometric pressure.

‡ Dry gas at 0°C and 760 mm Hg.

a Douglas bag. A special kymograph, electrically driven, records also the motion of the bell of the gasometer through an ink pen attached to the scale. Thus rate of respiration and volume of air ventilated during each of the five minutes of the recovery period can be easily read from the record. Basal ventilation is calculated from the average of two successive periods of ventilation of six minutes each, separated by a fifteen-minute interval of rest. During the performance of the exercise, the subject is connected to the Douglas bag, and at the end of the one-minute exercise period, while he resumes the recumbent position, the expired air is shunted to the Tissot gasometer through a three-way valve. All ventilatory volumes are measured as saturated gas, at 37°C and prevailing pressure.

In table 1 are tabulated the mean values and standard deviations obtained in a control group of 15 hospital patients without pulmonary or

cardiocirculatory disease, to serve as a basis for comparison with patients suffering from chronic pulmonary disease

### C *Breathing Reserve*

The *excess breathing capacity* beyond the *actual ventilation* in any given physical state is the *breathing reserve*. According to this conception, the maximum breathing capacity being in each subject a fixed value, the breathing reserve varies inversely with the breathing requirement, and for comparative purposes may be expressed in per cent of the maximum breathing capacity. Thus in a subject whose maximum breathing capacity = 150 liters per minute, and ventilation at rest = 5 liters per minute, the breathing reserve = 145 liters, and the ratio

$$\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100 \text{ at rest} = 145/150 = 96.6 \text{ per cent}$$

Similarly, in the same subject, if the ventilation during exercise = 25 liters per minute, the breathing reserve being 150 - 25 = 125 liters per

$$\text{minute, the ratio } \frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100 \text{ during exercise} = 125/150 = 83.3 \text{ per cent}$$

$$\text{D Ratio } \frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100 \text{ and Dyspnoea}$$

(1) In an analysis of 105 consecutive cases, the ratio  $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$  was calculated during each of

the five minutes following the completion of the standard exercise previously described, and the relation was established between this ratio and the ventilatory level at which dyspnoea develops. In 37 cases of this group no dyspnoea was experienced. Averaging the ratio

$$\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100 \text{ observed in each of these 37 cases}$$

during the first minute of recovery, it is shown that the mean breathing reserve, then at its lowest, is still 73 per cent of the maximum breathing capacity. In the remaining 68 cases (chart 1), in which dyspnoea was present for varying lengths of time, the average ratios

$$\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100, \text{ during the last minute preceding and}$$

the first minute following the cessation of dyspnoea, were respectively 63.2 and 71.5. Although the scattering of observations indicates that,

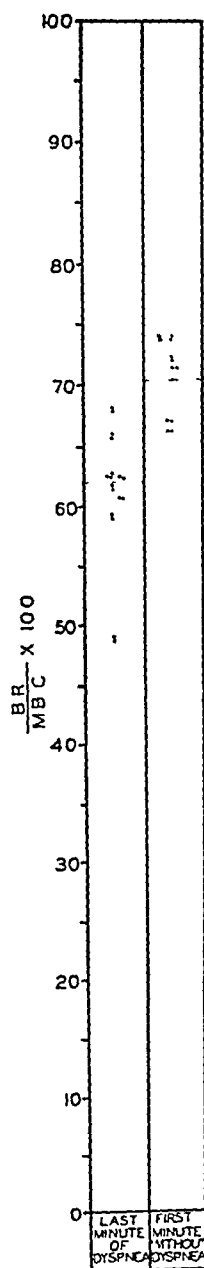


CHART 1

CHART 1 In each of 68 cases of chronic pulmonary disease manifesting the symptom of dyspnoea following the performance of a standard exercise, the ratios

$\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$  are plotted separately in two columns (1) on the left, during the last minute preceding the cessation of dyspnoea, (2) on the right, during the first minute following the cessation of dyspnoea. Mean values for the ratios are indicated by horizontal broken lines.

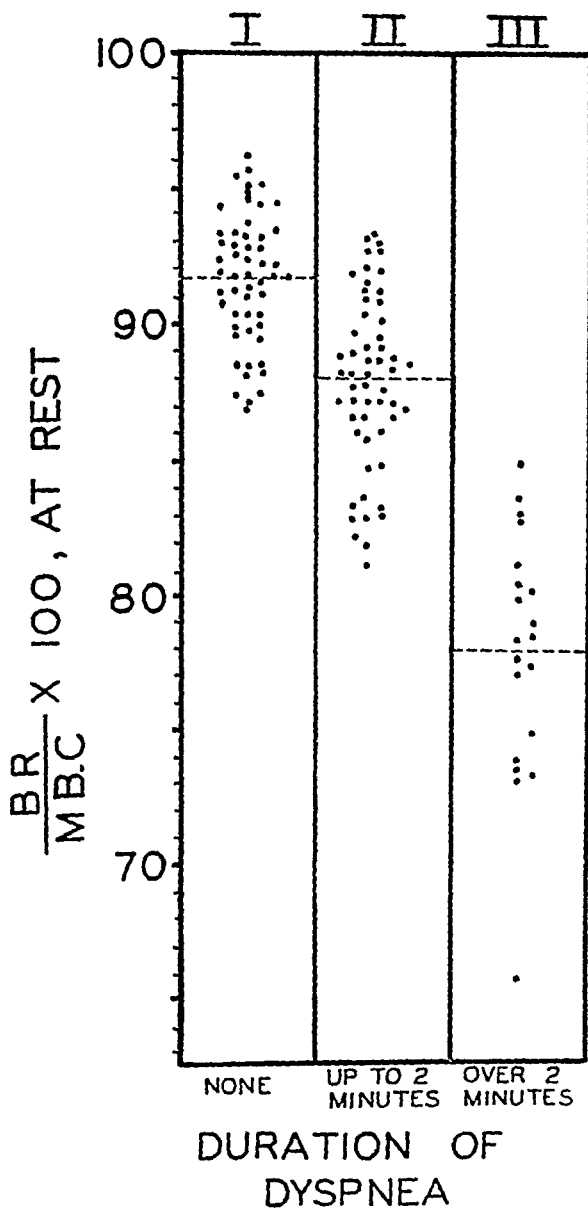


CHART 2

CHART 2 Ratio of  $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$  at rest in 129 cases of chronic pulmonary disease and its relation to the presence and duration of dyspnoea, observed during the recovery period following a standard exercise.

in a few instances, dyspnoea is still felt when the breathing reserve is 75 per cent of the maximum breathing capacity, it appears that the threshold of dyspnoea in the majority of cases is reached when the breathing reserve is between 60 and 70 per cent of the maximum breathing capacity

(2) It is obvious that the lower the ratio  $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$  at rest, the lower it will be during and after completion of the standard exercise. An attempt was made to establish a correlation between the ratio  $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$  at rest and the presence and severity of dyspnoea during the recovery period following exercise, in 129 patients, including the previous group, and in addition in some patients with chronic pulmonary disease, but without any clinical evidence of cardiocirculatory failure (chart 2). In 54 cases where no dyspnoea was felt during the recovery period, the average breathing reserve at rest was 91.7 per cent of the maximum breathing capacity with an S.D.  $\pm 2.4$ , in 55 subjects who were mildly dyspnoeic (less than two minutes of the recovery period), the average breathing reserve at rest was 88.0 per cent of the maximum breathing capacity, with an S.D.  $\pm 3.3$ , and in 20 cases where dyspnoea was of longer duration (two to five minutes, and in most instances from four to five minutes), the average breathing reserve was 77.9 per cent of the maximum breathing capacity with an S.D.  $\pm 4.5$ . Although there is some overlapping, especially between the nondyspnoeic and mildly dyspnoeic groups, comparison between groups I and II, and II and III, shows statistical differences between their respective means that are highly significant ( $P$  less than 0.01) (see footnote<sup>3</sup>).

The study of the scattering of observations shows distinctly that, when the ratio  $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$  at rest is above 93, no subject is dyspnoeic during the standard exercise test, between 92 and 87, one-half of the subjects are not dyspnoeic, the other one-half being dyspnoeic for less than two minutes, between 87 and 85, all were dyspnoeic up to two minutes, between 85 and 81, the subjects were either mildly or severely dyspnoeic, and finally below 80, the dyspnoea after the standard exercise lasted at least two minutes.

Estimation of the ratio  $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$  at rest in

gauging the extent of ventilatory insufficiency should yield valuable information. For example, if the limits within which this ratio decreases following thoracoplasty can be established, it should be possible to predict with some degree of accuracy before operation the degree of ventilatory insufficiency to be expected after its completion.

#### RESPIRATORY INSUFFICIENCY

Respiratory insufficiency is concerned with disturbance in the respiratory gas interchange between alveoli and the blood in pulmonary capillaries. This is dependent upon

- (a) The proportion of well, poorly and nonventilated alveoli
- (b) The number, size and distribution of capillaries in contact with alveoli, and the speed of blood flow through them
- (c) The gradient of pressure of respiratory gases across the alveolo-capillary partition, and the physical properties of this partition

Respiratory insufficiency may be present at rest or induced by exercise. It is often insidious and unrecognized. Cyanosis is its best known clinical manifestation. Yet the degree of anoxaemia and hypercapnoea (if present) and the defects in alveolar ventilation can only be determined by appropriate physiological measurements.

Determination of the *efficiency of alveolar ventilation* with regard to oxygen consumption and carbon dioxide elimination, and the study of *respiratory gases in the arterial blood*, will detect interference with respiratory gas exchange in the lungs, this may be present at rest or revealed only as the result of exercise.

#### A *Efficiency of Alveolar Ventilation*

The efficiency of ventilation with regard to respiratory gas exchange may be measured by the volume of oxygen removed from, or carbon dioxide eliminated in, each liter of air ventilated. (The terms of "rate of oxygen removal" and "rate of carbon dioxide elimination" will be used for the sake of simplification.)

Samples of gas collected in the Tissot gasometer and the Douglas bag, under basal conditions and during exercise, are analyzed in duplicate in the Haldane apparatus. The oxygen removed and the carbon dioxide eliminated are expressed as the number of cubic centimetres of gas exchanged, per liter of air ventilated. Oxygen intake and carbon dioxide output are also calculated per minute per square metre of body surface (table 1).

In table 2, data found in the literature have been tabulated (11, 12, 7) To fit the simpler expression that we adopted from Herbst (1928), the "ventilatory equivalent," used by most authors since Anthony, has been recalculated as follows If ventilatory equivalent =  $\frac{100}{\text{O}_2 \text{ consumed}}$ , then rate of oxygen removal =  $\frac{100}{\text{Ventilatory equivalent}}$  It will be seen that when the rate of oxygen removal is determined by gas analysis, the co-

TABLE 2

*Oxygen consumption and carbon dioxide elimination per liter of ventilation at rest  
A review of values found by various authors in normal or control subjects\**

AUTHORS	NUMBER OF SUBJECTS	METHOD OF DETERMINATION	MEASUREMENT			
			O <sub>2</sub> , cc /lit vent		CO <sub>2</sub> , cc./lit vent	
			Mean	Coeff of variation	Mean	Coeff of variation
			cc	per cent	cc	per cent
Knipping & Moncreff	54	Spirometric tracings	41 0	25†	—	—
Hurtado & Boller	15	Spirometric tracings	37 5	27	—	—
Kaltreider & McCann	20	Gas analysis	41 7	—	—	—
McMichael	76	Gas analysis	44 0‡	16	36 0	14
Cournand & Richards	15	Gas analysis	46 8§	15	36 3§	16

\* Values expressed as ventilatory equivalent for

$$\text{Oxygen (or CO}_2\text{)} = \frac{\text{Min Vol Ventil} \times 100}{\text{Min Vol Ventil} \times \text{O}_2\% \text{ Intake}} = \frac{100}{\text{O}_2\% \text{ Intake}}$$

† Approximate

‡ Approximate (assuming room temperature to be 25°C, but calculated as dry gas at 0°C and 760 mm Hg)

§ Calculated as dry gas at 0°C and 760 mm Hg

efficient of variation around the mean is only about 15 per cent, as against a variation two-thirds greater when determined from spirometric tracings Furthermore, Kaltreider and McCann (7) have shown a definite relationship between this measurement and the degree of disability observed in pulmonary fibrosis, emphysema and cardiac insufficiency As an index of adequate relationship between alveolar ventilation and pulmonary circulation, McMichael (13) considers the rate of oxygen removal to be of significant value

During exercise, many factors may influence the changes observed in this measurement, chiefly, of course, the severity of the exercise. It is generally assumed (14) that the relation between pulmonary ventilation and carbon dioxide eliminated is nearly linear, so that the rate of carbon dioxide elimination per liter of ventilation varies very little (*a*) from rest to exercise, and (*b*) in relation to the intensity of exercise. In contrast (14), the oxygen consumption is much more dependent upon the rate of circulation and is limited by it. In our standard exercise of short duration (one minute), the rate of pulmonary circulation probably increases at first much more rapidly than the pulmonary ventilation, which explains in part the notable increase in the rate of oxygen removal observed (from an average of 46.8 to an average of 54.8). If, however, large areas of the lungs during exercise are ventilated but not circulated, this index should remain as it is at rest, or actually decrease. On the other hand, if as a result of cardiac insufficiency the cardiac output does not increase proportionally to the ventilation during exercise, the same result should obtain. Although somewhat ambiguous on that account, and requiring a careful analysis of other factors involved, the variation of the rate of oxygen removal at rest and during standard exercise may lead to valuable information concerning the relation between pulmonary ventilation and pulmonary circulation. It should be further noted that nervous and reflex factors may also increase ventilation (and decrease rate of oxygen removal), independent of the pulmonary and circulatory state.

### B *Respiratory Gases in Arterial Blood*

Adequate correlation between alveolar ventilation and pulmonary capillary perfusion is reflected in a high percentage of haemoglobin in the oxyhaemoglobin state in the arterial blood, whether at rest or following exercise. In table 3, results in 15 control subjects with no pulmonary or circulatory disease are computed during rest and following standard exercise. The average values and variations at rest are in harmony with those observed by Dill, Edwards and Consolazio (14) in male subjects aged twenty-three to forty-five at rest. Following exercise, these values remained unchanged, confirming the conclusions of Himwich and Barr (1923) that even during severe exercise the oxyhaemoglobin saturation per cent does not fall below 95.

A decrease in arterial oxygen saturation, below normal limits, may be due to one of several causes. The most important, in chronic pulmonary

disease, is the arterial anoxaemia brought about when pulmonary blood flows through the capillaries of alveoli that are unventilated, or inadequately ventilated. Of less importance in pulmonary disease, though probably more so in cardiac failure, is the arterial anoxaemia produced by impaired diffusion of oxygen from alveoli to intracellular haemoglobin, due to congestion, oedema or other causes. A third factor, also more significant in heart disease, is retarded circulation causing pulmonary blood to be greatly unsaturated when it reaches the alveoli, and a fourth, true "shunting" of pulmonary blood from pulmonary arteries to veins by passage through vessels that have no access to pulmonary air spaces.

TABLE 3

*Arterial blood studies in a control group at rest and during early period of recovery following standard exercise\**

	REST		RECOVERY	
	Mean	Standard deviation	Mean	Standard deviation
O <sub>2</sub> Haemoglobin Capacity, vol %	17.1	±1.9	17.9	±1.7
O <sub>2</sub> Haemoglobin Content				
$\frac{\text{O}_2 \text{ Haemoglobin Capacity}}{\text{O}_2 \text{ Haemoglobin Content}} \times 100$	96.2	±1.2	95.8	±1.3
CO <sub>2</sub> Content, vol %	52.0	±2.4	47.8	±2.3
pCO <sub>2</sub> , mm Hg	43.7	±3.5	43.0	±2.4
CO <sub>2</sub> Content at 40 mm Hg, vol %	50.6	±2.3	46.6	±1.9
pH <sub>s</sub> †	7.43	±0.02	7.40	±0.03

\* See table 1

† At 38°

There is also a tendency in normal individuals for maintenance of a constant level of carbon dioxide tension in the arterial blood, and a constant hydrogen ion concentration. This is shown in table 3. With exercise of the limited degree described, normal subjects usually show an appreciable drop in arterial carbon dioxide content, little change in carbon dioxide pressure and a small decrease in pH. There may be, however, considerable variations in these responses, even in normal subjects, due to differences in muscular development, in breathing facility, and above all in the state of physical training. The latter may affect to a marked degree the ease and efficiency of circulatory and respiratory adaptation to exercise, blood carbon dioxide levels and arterial pH are often sensitive indices of such adaptation. For example, a poorly



trained individual often shows a large increase in carbon dioxide tension after exercise, with corresponding sharp drop in arterial pH an evidence of ineffectual cardiopulmonary adjustment

Samples of arterial blood for respiratory gas analysis are secured at rest, and at the end of the first minute of recovery, by puncture of the brachial artery. A careful local anaesthesia, and a sharp, flat-bevel, 19-gauge needle are used in order to obtain a painless, easy puncture. The samples of blood drawn under oil are transferred into chilled bottles containing 0.6 mg of sodium fluoride and 4.5 mg of neutral potassium oxalate dried in autoclave. The blood is gently stirred and the pipettes for determination of oxygen and carbon dioxide content are immediately filled and analyzed in duplicate in the Van Slyke manometer. Methods for determination of oxygen capacity and carbon dioxide dissociation curves, from which  $p\text{CO}_2$  and pH may be estimated, have been described in detail elsewhere (16).

#### CARDIOCIRCULATORY INSUFFICIENCY

Cardiocirculatory insufficiency, in various combinations with ventilatory and respiratory insufficiency, in the course of chronic pulmonary disease and collapse therapy, may be due to

- (a) Hypertension in the lesser circulation from any cause and subsequent right ventricular hypertrophy and failure
- (b) Obstruction to the flow of blood by displacement and torsion of the heart and intrathoracic vessels, increased pressure in the thoracic cavity, or disturbed mechanics of breathing. These changes may influence the cardiac output, the speed of circulation and favor pulmonary congestion
- (c) The effects of anoxaemia upon the cardiac muscle and upon the cardiovascular centres
- (d) Independent cardiac disease

The measurement of the arterial blood pressure, the venous pressure, pulse rate, circulation time and the vital capacity, both at rest and following increase of the blood volume by a rapid saline infusion (17, 18), and the electrocardiogram are the chief data which we have used to estimate cardiocirculatory performance. In some instances these measurements may be repeated following exercise.

The technique is carried out as follows

The patient being in a nearly recumbent position, the venous pressure apparatus of the water-manometer type is connected to the side opening of a

three-way stopcock The zero point for venous pressure is taken arbitrarily as a level 5 cm below the angle of Louis The circulation time is measured from arm to carotid sinus (NaCn) (21), or from arm to tongue (calcium gluconate) (22) Vital capacity is obtained by having the subject connected to a Benedict-Roth metabolism apparatus, and recording several tracings of maximal breaths

The artificial increase of blood volume (19) is produced by infusion of 1,500 cc of an isotonic saline solution in 30 minutes, the infusion tubing being connected to the three-way stopcock Venous pressure, circulation time and vital capacity are measured before the infusion is started and at the end of the infusion The variations in venous pressure are followed closely, by measuring its level every two minutes

The normal range of venous pressure lies between 30 and 100 mm of water Altschule (20), in a group of 83 normal subjects, found the venous pressure to lie below 100 mm in all cases but 3 This coincides with our experience, and 100 mm water can be assumed to represent the upper limit of normal venous pressure Sufficient time (at least five minutes) must be allowed to elapse between the insertion of the needle (gauge 17) and the reading Following the 1,500 cc infusion in normal subjects, the level of venous pressure increases but little, at most 30 to 35 mm water, and remains below 100 mm water If the rise is greater, it is thought to represent failure of the right heart to accommodate an increase in blood volume

The high limit of normal of the circulation time is considered to be eighteen seconds (21) Following the infusion test, it hardly changes more than one or two seconds in normal subjects, a prolongation over five seconds is considered abnormal

Decrease of the vital capacity following the infusion test is evidence of pulmonary congestion This may be related to the failure of the left heart to accommodate an increase in blood volume, or to other causes affecting the flow of blood in the pulmonary veins, or to the vasomotor state of the pulmonary capillaries In normal subjects the per cent decrease from pre-infusion values is insignificant More than an 8 per cent decrease can be considered as an evidence of pulmonary congestion

#### SUMMARY

A simple classification of pulmonary insufficiency is offered This consists of the division into ventilatory insufficiency, respiratory insufficiency and forms associated with cardiocirculatory insufficiency

Physiological principles involved in this differentiation and methods of measurement are reviewed and discussed

Ventilatory insufficiency is measured by decrease in maximum breathing capacity, or more exactly decrease in breathing reserve. The relation existing between breathing reserve and dyspnoea in pulmonary disease is stressed

Respiratory insufficiency is indicated by (a) decrease in arterial oxygen saturation, (b) decrease in percentage removal of oxygen from inspired air or percentage elimination of carbon dioxide in expired air

In addition to the recognized tests of cardiac function, latent cardio-circulatory insufficiency may be revealed by simultaneous measurements of the blood pressure, venous pressure, circulation time and vital capacity before and following a rapid saline infusion

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a month before hospital admission (to St. Thomas' Hospital, London) and two weeks later there had been a small haemoptysis and some dyspnoea on exertion. Sputum had failed to show tubercle bacilli on concentration and chest X-rays had revealed merely a slight evidence of the mediastinal shadow, lung fields being normal with no evidence of tumor. Right artificial pneumothorax was induced with a view to thoracoscopy but the apical and mediastinal surfaces were adherent. Exploratory thoracotomy showed the superior vena cava as a hard band running from the root of the neck into the right auricle and no constricting bands or tumor were found. Signs of obstruction were somewhat less evident four

months later. It was thought that the lobar pneumonia might have been a factor by setting up a mediastinitis. The ultimate prognosis is generally regarded as unfavorable, improved circulation being possible only by canalization of the clot, but in this case the immediate prognosis seemed good. Treatment of the condition is discussed, especially radical removal of tumors and constricting bands, and palliative treatment of some cases by mediastinal decompression which is justifiable where pressure increases sufficiently to cause collapse of softer structures. Exploratory thoracotomy is advised in cases of doubtful aetiology.—*Thrombosis of the Superior Vena Cava, E. M. Buzzard, Tubercle, January, 1940, 34: 39.*—(A. P.)

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## THROMBOSIS OF THE PULMONARY ARTERY<sup>1 2</sup>

J WOODROW SAVACOOOL AND ROBERT CHARR

In the present communication are reported certain observations concerning the right-sided preponderance of antemortem thrombosis of the pulmonary artery in tuberculous patients

*Material* The material studied consists of 12 tuberculous patients who showed massive thrombosis of the pulmonary artery at autopsy. In addition, 88 cases reported in the literature by 52 authors (2 to 56) are briefly reviewed. The résumé of the clinical and pathological findings of these hundred cases are listed in tables 1 and 2.

Only cases with a large thrombus, almost or completely occluding the main trunk of the pulmonary artery or its main branches, were included in this study. The thrombus was designated as right or left-sided only when it was definitely unilateral. When the thrombus had extended into the trunk from one artery it was classified as one-sided, whereas if it extended into both arteries as well as the trunk, it was considered bilateral.

*Findings* In our series of 12 cases, 8 showed thrombi in the right pulmonary, only 2 in the left pulmonary artery, and 2 in both arteries. There seems to be no doubt as to their being antemortem thrombi. Their gross shape and size in relation to the lumen and shape of the involved arteries, the tenacity of their adherence to the intima of the vessels, invasion of the thrombi by strands of connective tissue from the intima and the general histological structure of the deposition of the platelets, fibrin and other cellular elements of the blood excluded any possibility of these being emboli or postmortem thrombi.

The primary site of thrombosis in these cases appeared to be the terminal ends of the first branches of the main pulmonary artery. Often the first branch of the pulmonary artery was imbedded in the area of tuberculous consolidation or firmly encased within the fibrotic walls of

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tuberculous cavities Histological examination of these thrombi showed that the terminal portions of the thrombi appeared older, suggesting that

TABLE 1

CASE NUMBER	AGE	SEX	AUTOPSY NUMBER	LOCATION OF THROMBI	PRINCIPAL DIAGNOSIS	REMARKS
1	58	M	251	Main trunk and both arteries	Anthracosilicosis, pulmonary tuberculosis	Thrombosis and endarteritis obliterans of vessels near right upper lobe cavity
2	62	F	357	Left artery	Pulmonary tuberculosis	Diffuse fibrosis of left lung, disease older than on right side
3	32	F	361	Right artery	Pulmonary tuberculosis	Giant cavity in right lung
4	47	M	363	Right artery	Anthracosilicosis, pulmonary tuberculosis	
5	58	M	371	Right upper lobe branch	Anthracosilicosis, pulmonary tuberculosis	Cardiac hypertrophy Thrombus extended from tuberculous cavity
6	60	M	375	Right artery	Anthracosilicosis	Cardiac hypertrophy Infarcts in right lower lobe
7	45	M	367	Right upper lobe branch	Anthracosilicosis, pulmonary tuberculosis	Extensive cavity in right upper lobe
8	56	M	400	Right upper lobe branch	Anthracosilicosis, emphysema and fibrosis	Progressive right ventricular failure
9	31	M	402	Right artery	Anthracosilicosis, pulmonary tuberculosis	Thrombi older in smaller pulmonary vessels Myocardial degeneration
10	52	M	421	Right artery	Anthracosilicosis, pulmonary fibrosis and tuberculosis	Myocardial degeneration and aortic dilatation
11	37	F	430	Left artery	Pulmonary tuberculosis	Left pneumothorax five years with uncollapsed cavity Marked left-sided fibrosis
12	44	F	450	Left upper lobe and right upper lobe branches	Pulmonary tuberculosis	Cardiac hypertrophy and dilatation Right ventricular mural thrombus

the thrombi began in the terminal ends and gradually grew toward the main trunks In all our cases the thrombi were on the side in which the pulmonary disease was more marked In 2 of our cases in which the

TABLE 2

AUTHOR AND YEAR	AGE AND SEX	LOCATION OF THROMBI	PRINCIPAL DIAGNOSIS	REMARKS
Hebe (2) (1837)	65 F	Main trunk and both arteries	Cardiac failure	Cardiac hypertrophy and chronic passive congestion
Kidd (3) (1856)	26 F	Left lower lobe branch. Small thrombi in both arteries	Lung abscess in right lower lobe	Postpartum two weeks at onset of symptoms. Died two weeks later.
Blachez (4) (1866)	29 F	Right artery	Rheumatic fever and pericarditis	Right ventricle dilated and hypertrophied
Elbogen (5) (1881)	44 M	Main trunk	Pulmonary arteriosclerosis	Right side of heart dilated and hypertrophied. Pulmonary artery dilated
Ferraro (6) (1886)	23	Right artery	Mitral stenosis	Cardiac failure
Dickinson (7) (1897)	4½ M	Main trunk and both arteries	Congenital heart disease	Congenital pulmonary stenosis and patent interventricular septum
von Jurgenson (8) (1899)	60 M	Both arteries	Emphysema	
McPhedran and MacKenzie (9) (1903)	55 M	Branches to right lower and middle lobes	Emphysema, arteriosclerosis, chronic pneumonia in right lower lobe	Jaundice, syphilis of liver, infarction in right lower lobe. Possible syphilis of pulmonary artery
Hart (10) (1905)	F	Main trunk and both arteries. Older on right	Mitral stenosis	Marked cardiac hypertrophy. Thrombi in right auricle
Hart (10) (1905)	M	Main trunk and right artery	Pyelonephritis, tabes dorsalis	Thrombus in left crural vein. No pulmonary pathology noted
Monckeberg (11) (1907)	56 M	Main trunk and right artery, small left branch	Pulmonary arteriosclerosis	Right ventricular hypertrophy. Thrombus in vena cava. Cardiac decompensation
Ittameier (12) (1907)		Right branch	Aortic stenosis and insufficiency	Emphysema

TABLE 2—*Continued*

AUTHOR AND YEAR	AGE AND SEX	LOCATION OF THROMBI	PRINCIPAL DIAGNOSIS	REMARKS
Nedderison (13) (1908)		Right and left branches	Mitral stenosis and insufficiency, pulmonary arteriosclerosis	
Kraus (14) (1909)	30 M	Main trunk and right artery		Right ventricular hypertrophy and dilatation
Stadelmann (15) (1909)	27 M	Both arteries and branches	Pulmonary arteriosclerosis, mitral stenosis and insufficiency	Cardiac decompensation Believes thrombosis started from sclerosis
Funke (16) (1910)	M	Right artery	Pulmonary tuberculosis	Cyanosis and swelling of face, neck and arm, worse on right
Funke (16) (1910)	35 M	Right artery	Gangrene of foot, general paresis	Thrombus terminal complication
Smith (17) (1913)	50 M	Main trunk, both main arteries, right ventricle	Anthraxosis, pulmonary tuberculosis, chronic nephritis	Thrombi separate, one side from the other
Hoffmann (18) (1916)	39 M	Main trunk and right artery	Pulmonary atheromatosis	Right heart hypertrophied Pulmonary artery dilated
Lutembacher (19) (1917)	32 F	Right artery	Mitral stenosis, patent foramen ovale	Right heart dilated Thrombus in inferior vena cava and right auricle
Letulle and Jacquelin (20) (1920)	58 M	Right artery and branches	Pulmonary tuberculosis, right apical cavity, aneurysm of pulmonary artery	Syphilis also present
Billings (21) (1921)	60 M	Both arteries	Myocardial degeneration, left pulmonary infarct	Bilateral hydrothorax
Billings (21) (1921)	60 M	Both arteries and branches	Chronic nephritis and arteriosclerosis	Right hemiplegia Cardiac decompensation
Billings (21) (1921)	F	Right smaller branches	Acute nephritis, myocardial degeneration	Postpartum one month at onset of symptoms



TABLE 2 *Contd.*

Author and Year	Age Sex	Location of the lesion	Pathological process	Remarks
Hippen (21) (1921)	60 M	Left lower lobe branch	Acute pleurisy, massive consolidation, gangrenous necrosis	Thrombosed external jugular vein
Lowter (22) (1922)	50 F	Right artery	Irregular aneurysm	Pneumothorax, pleurisy and pulmonary infarct
Loewen (23) (1922)	51 M	Both arteries and branches	Patent foramen ovale	Cardiac symptoms none
Herrman (24) (1923)	35 F	Both arteries and branches	Cardiac failure, pulmonary infarct	Acute pleurisy, basal Cardiac enlargement
Allbutt (25) (1924)	M	Main trunk	Pneumothorax resolution	Sudden death following development of symptoms over one week
Linn (26) (1924)	81 M	Main trunk and right artery	Healed tuberculous chronic purulent bronchitis—right	Thrombus in right renal artery and aorta. Dilated right heart
Rodshirox and Pernmond (27) (1925)	56 M	Right artery	Bronchitis and emphysema	Right ventricular dilatation and hyper trophy. Pulmonary artery dilated
Schramm (28) (1927)	49 F	Right artery extending into lower lobe branch	Pulmonary atherosclerosis, mitral stenosis	Dilated pulmonary artery
Pick (29) (1927)	64 F	Main trunk and both arteries	Mitral stenosis and insufficiency	Pulmonary infarct. Thrombus in aorta and iliac arteries
Ljungdahl (30) (1928)	51 F	Right artery and branches	Pulmonary sclerosis	Right heart enlarged
Ljungdahl (30) (1928)	38 F	Right artery	Cardiac decompensation, syphilis	Right heart dilated and hypertrophied
Samck (31) (1928)	63 F	Right and left branches	Right pleural effusion, dilated right heart	Thrombus—left renal and right femoral veins
Meldolesi and Dionisi (32) (1929)	25	Right artery	Mitral stenosis	Cardiac failure
Barnes and Yater (33) (1929)	34 M	Both arteries, larger on right	Bronchiectasis, lung abscess—right upper lobe	Thrombus believed two years old. Syphilis also present

TABLE 2—*Continued*

AUTHOR AND YEAR	AGE AND SEX	LOCATION OF THROMBI	PRINCIPAL DIAGNOSIS	REMARKS
Jump and Baumann (34) (1929)	48 M	Main trunk and both arteries	Pulmonary tuberculosis and atherosclerosis of pulmonary artery	Cardiac failure Dilatation of right ventricle and pulmonary artery
Goedel (35) (1930)	59 M	Main trunk and right artery	Cardiac failure	Right ventricle enlarged
Goedel (35) (1930)	50 M	Medium sized branches right and left		
Arrigoni (36) (1930)	63 F	Both arteries	Mitral endocarditis and stenosis, pulmonary arteriosclerosis	Thrombi in right femoral artery and vein
Desclm (37) (1930)	41 M	Both arteries and branches	Carcinoma of mediastinal lymph nodes	Old thrombus in right femoral vein Small thrombi in right ventricle
Desclm (37) (1930)	62 F	Main trunk and both arteries		
Desclm (37) (1930)	45 F	Right artery and small left lower lobe branch		Thrombosis of right femoral vein Cardiac enlargement
Desclm (37) (1930)	49 F	Right artery and left upper lobe branch	Thrombophlebitis of both lower extremities	Right ventricular hypertrophy
Desclm (37) (1930)	65 F	Right artery	Mitral stenosis and insufficiency	Thrombosis left femoral vein
Desclm (37) (1930)	58 F	Right artery and branches	Carcinoma of oesophagus	Both femoral veins thrombosed
Desclm (37) (1930)	56 F	Both upper lobe branches	Carcinoma of breast	Postoperative death
Desclm (37) (1930)	45 M	Both branches	Right lower lobe lung abscess and peripheral gangrene, syphilitic aortitis	Both femoral veins thrombosed
Desclm and Regnier (38) (1931)	53 M	Right artery		Cardiac degeneration and hypertrophy Dilatation of right heart especially Femoral thrombosis bilaterally

TABLE 2—*Continued*

AUTHOR AND YEAR	AGE AND SEX	LOCATION OF THROMBI	PRINCIPAL DIAGNOSIS	REMARKS
Desclin and Regnier (38) (1931)	55 M	Main trunk and both arteries	Bronchopneumonia, small lung abscess	Femoral thrombosis No cardiac involvement
Means and Mallory (39) (1931)	60 M	Right artery	Arteriosclerotic heart disease	Cardiac dilatation and hypertrophy Bronchial arteries hypertrophied
Brenner (40) (1931)	58 F	Right lower lobe branch and small branches	Chronic bronchitis and emphysema	Right ventricular dilatation and hypertrophy Infarct in right lower lobe
Brenner (40) (1931)	49 F	Both lower lobe branches	Old rheumatic fever, chronic bronchitis and emphysema	Cardiac hypertrophy and dilatation
Brenner (40) (1931)	58 M	Bilateral small branches	Chronic bronchitis and emphysema	Dilatation of pulmonary artery Cardiac hypertrophy Coronary and pulmonary sclerosis
Brenner (40) (1931)	56 M	Right lower lobe branch	Gastric carcinoma, chronic bronchitis and emphysema	Died without operation Dilatation and atheromatosis of pulmonary artery
Brenner (40) (1931)	46 F	Right lower lobe branch	Mitral stenosis	Atheroma in pulmonary artery Cardiac hypertrophy, more marked on right side
Brenner (40) (1931)	60 M	Branches to right upper and lower and left lower lobe	Chronic bronchitis and emphysema, arteriosclerosis	Pulmonary artery dilated and atheromatous
Boswell and Palmer (41) (1931)	39 M	Right artery with extension to left	Acute respiratory infection	Peripheral and left parts of thrombus newer Thrombosis probably began with infection
Lutembacher (42) (1933)	20 M	Right artery	Mitral stenosis and pulmonary arteritis	Pulmonary infarcts Dilated right ventricle

TABLE 2—Continued

AUTHOR AND YEAR	AGE AND SEX	LOCATION OF THROMBI	PRINCIPAL DIAGNOSIS	REMARKS
Iowler (43) (1931)	52 M	Both arteries	Chronic bronchitis	EKG—inverted T-wave in II and III Right axis deviation
Kampmeier (44) (1934)	16 F	Right artery and right lower lobe branches	Mitral stenosis, patent foramen ovale	Right heart dilated Thrombus in inferior vena cava and right auricle
Montgomery (45) (1935)	36 F	Both arteries	Pleurisy, Ayerza's syndrome	History of symptoms since delivery eight years previously Heart failure
Sprague and Mallory (46) (1936)	50 F	Both arteries and branches	Pulmonary endarteritis and cor pulmonale	
Ameuille <i>et al</i> (47) (1936)	35 M	Right lower lobe branch	Pulmonary tuberculosis both upper lobes	Intestinal tuberculosis Partly organized atelectatic area in right lower lobe
Ameuille <i>et al</i> (47) (1936)	35 F	Main trunk and both arteries	Pulmonary tuberculosis	Grunt cavity in left upper lobe
Ameuille <i>et al</i> (47) (1936)	36 M	Left lower lobe branch	Pulmonary tuberculosis	Intestinal tuberculosis
Lutembacher (48) (1937)	36 M	Right artery	Mitral stenosis, pulmonary arteritis	Pulmonary artery dilated Pulmonary infarcts
Lutembacher (48) (1937)	35 F	Both arteries and lower lobe branches	Mitral stenosis	Pulmonary artery dilated Atelectasis of part of left lower lobe
Lutembacher (48) (1937)	32 F	Right artery	Mitral stenosis	Right ventricle dilated and hypertrophied
Mohler and Crawford (49) (1937)	40 F	Left lower lobe branch	Mitral stenosis	Cardiac hypertrophy and multiple pulmonary infarcts
Mohler and Crawford (49) (1937)	50 F	Left artery	Congestive heart failure, myocardial fibrosis	Multiple small infarcts
Mohler and Crawford (49) (1937)	52 F	Right lower lobe branch	Cardiac hypertrophy	Congestive heart failure
Mohler and Crawford (49) (1937)	64 M	Right artery	Anthraxis, pulmonary fibrosis	Cardiac hypertrophy and dilatation

TABLE 2—*Concluded*

AUTHOR AND YEAR	AGE AND SEX	LOCATION OF THROMBI	PRINCIPAL DIAGNOSIS	REMARKS
Mohler and Crawford (49) (1937)	52 F	Right artery	Hypertension, obesity, fibromyomata	Cardiac hypertrophy Thrombi of right femoral and iliac veins Empyema
Mohler and Crawford (49) (1937)	16 F	Bilateral smaller branches	Pulmonary abscess—left lower lobe	Right artery compressed by growth
Mohler and Crawford (49) (1937)	50 M	Right artery	Pulmonary carcinoma	Small infarct Thrombus in right auricle
Mohler and Crawford (49) (1937)	40 F	Right artery	Pneumonia and left empyema	Tuberculous changes in vessel wall Aneurysm of pulmonary artery in right lower lobe branch
Arel and Saka (1937)	54 M	Right artery, branch on left	Pulmonary tuberculosis	Patent foramen ovale Dilated pulmonary artery
Liebermeister (1937)	47 M	Both arteries	Mitral stenosis, pulmonary tuberculosis and bilateral pneumothorax	Right heart hypertrophy Terminal jaundice and pulmonary infarct
Markoff (52) (1938)	34 M	Right artery	Mitral stenosis and insufficiency	Terminal gangrene—right upper lobe
Markoff (52) (1938)	59 F	Right branches	Purulent bronchitis, myocardial degeneration	Possibly small emboli with gradual accretion Post-partum death
Barsoum (53) (1938)	31 F	Main trunk and both arteries	Paroxysmal tachycardia	Pulmonary fibrosis
Barsoum (53) (1938)	50 F	Main trunk and both arteries	Chronic bronchitis, pulmonary atherosclerosis	Popliteal phlebitis
Means and Mallory (54) (1938)	71 M	Right lower and upper lobe branches, left smaller branches	Pulmonary thrombosis	Thrombus in inferior vena cava
Manaugh (55) (1939)	60 M	Right artery extending into middle and lower lobe branches	Chronic arthritis	Thrombus in right auricular appendage Mistaken for coronary attack
Wade (56) (1940)	59 M	Main trunk and both arteries, separate thrombi	Pulmonary anthracosis and fibrosis, cardiac hypertrophy	EKG—inverted T-wave in leads II, III, and IV Right heart dilated

thrombi were on the left side, one had had artificial pneumothorax on that side for five years and the other showed marked fibrosis of the left lung as the result of pleural effusion on that side

In 2 cases in which the thrombi were on both sides, the thrombus on the right side looked older both grossly and histologically. In these cases the tuberculosis was more advanced and chronic on the right side. Evidently the thrombus formed first on the right side and later extended into the left side.

Among the 88 cases collected from the literature (table 2) the thrombi were in the right pulmonary artery in 41, in the left pulmonary artery in 4 and in both arteries in 43. Regarding the cases of bilateral thrombosis, several authors stated that the thrombi on the right side appeared older. Myocardial insufficiency appeared to be more frequently associated with bilateral thrombosis.

#### DISCUSSION

In the entire series of 100 cases, 49 showed thrombosis on the right side, 45 on both sides and only 6 on the left side. The preponderance of thrombosis in the right pulmonary artery or the infrequency of this condition on the left side may be dependent upon certain anatomical differences about the roots of the lungs (figures 1 and 2). On the right side, according to Senior (57), the pulmonary artery is longer than the left and lies horizontally under the arch of the aorta. In its course to the hilum, the right pulmonary artery has certain structures close to it which the left artery does not possess. In front there is the ascending aorta and the superior vena cava, as well as the phrenic nerve, anterior pulmonary plexus and the reflexion of the pleura. Lying close to the artery posteriorly is the right bronchus and the azygos vein. Below the artery is the right atrium and the upper right pulmonary vein. Above the artery is the arch of the aorta. At the root of the lung, the right bronchus is above and behind it and the pulmonary veins below and in front of it.

On the other hand, the left pulmonary artery does not have such close relationship to the various structures. It is shorter and slightly smaller and passes in front of the descending aorta. At the root of the lung the left bronchus lies below and behind the artery and the pulmonary veins lie in front (figures 1 and 2). The left pulmonary artery does not have the ascending aorta and superior vena cava in front as has the right pulmonary artery. Neither has it the arch of the aorta above it and the

FIG 1

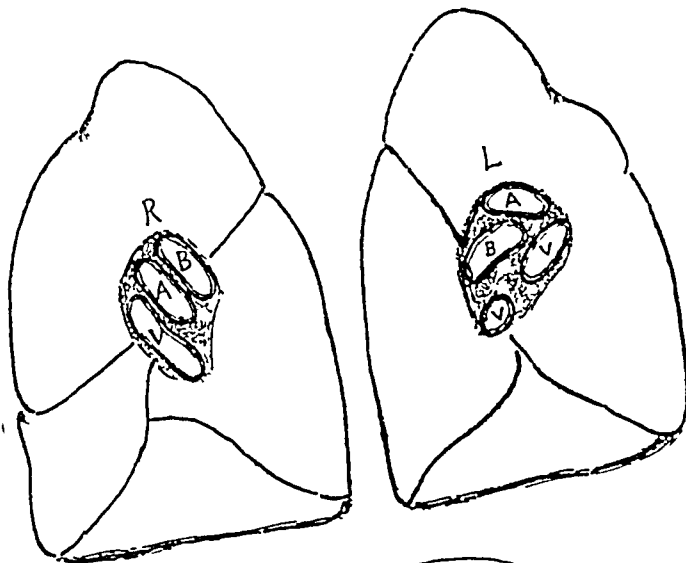


FIG 2

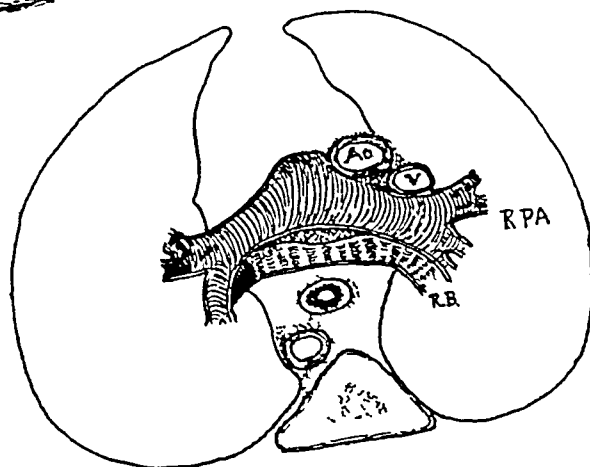
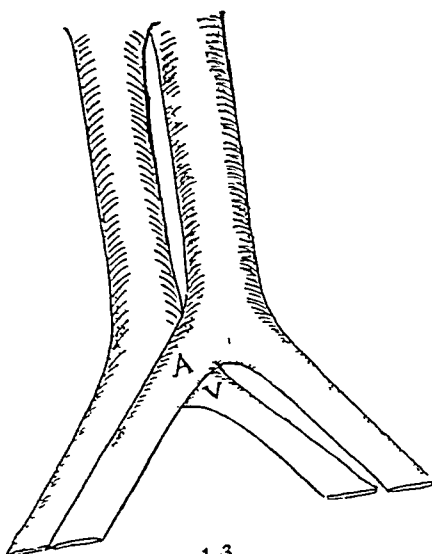


FIG 3



FIGS 1-3

left atrium and the right pulmonary veins below it as has the right pulmonary artery. So, too, the azygos vein which lies behind the right pulmonary artery is not present on the left side.

For these reasons the left pulmonary artery may be less influenced by pathological conditions of the lungs and aorta. In chronic pulmonary tuberculosis there is frequently marked traction upon and distortion of the trachea and bronchi and in cardiovascular disease the aorta is occasionally enlarged or sometimes displaced. Such processes would have much more effect on the right pulmonary artery than on the left, since the aorta arches over the right and is unrelated to the left artery, the right bronchus is more nearly adjacent to the right artery than the left bronchus is to the left artery. Other structures such as the right atrium and superior vena cava may also be of importance in this connection. External pressure from contiguous structures may produce narrowing of the arterial lumen, thus reducing the velocity of blood flow and aiding thrombosis.

Substantiating the above view that an artery lying over a vein may slow up the velocity of blood flow, thereby aiding thrombosis, are several cases of unilateral oedema of the ankles in pulmonary tuberculosis observed by us. In these cases the swelling was present only in the left ankle and leg. There were patients with bilateral swelling of the legs and, even among these, the oedema was more marked on the left side. Of five autopsied cases, one showed a large antemortem thrombus in the left common iliac vein above and below the point over which the right common iliac artery crossed.

It seems that the pressure exerted upon the left common iliac vein by the right common iliac artery at the point of crossing (figure 3) narrows the lumen of the vein, thereby slowing the venous blood flow and favoring thrombus formation. Slowing of blood flow with definite pooling or stagnation of the blood-stream, resulting either from pressure upon the vessel or from constriction of the blood vessel by intrinsic vascular disease, has been considered by Aschoff (58) as a definite aetiological factor in thrombosis.

FIG. 1. Schematic drawing of the right (R) and left (L) hilum regions showing the relations of the pulmonary arteries (A) to the bronchi (B) and the pulmonary veins (V). On the right side pulmonary artery is "squeezed" between the bronchus and pulmonary vein.

FIG. 2. Schematic drawing of the cross section through the roots of lungs showing the aorta (Ao) and superior vena cava (V) anterior to the right pulmonary artery (RPA) and the right bronchus (RB) behind it.

FIG. 3. Schematic drawing of the right common iliac artery (A) crossing over the left common iliac vein (V), interfering with the venous blood flow through the left common



Several authors mentioned that among the cases of bilateral thrombosis, the thrombus on the right side looked older. This certainly was so in our 2 cases. From this we have inferred that, probably in a considerable number of cases of bilateral thrombosis, the thrombus on the left side was the continuation or extension of the thrombus in the right pulmonary artery. The frequent association of myocardial insufficiency with bilateral thrombosis suggests that lack of propelling force of the blood-stream tends to encourage relatively rapid development of the thrombus into the trunk and left pulmonary artery.

In our earlier study (1) we have reviewed various hypotheses advanced in regard to the pathogenesis of thrombosis of the pulmonary artery. Degeneration and inflammation of the artery, endarteritis, chemical changes of the blood due to the destruction of the pulmonary tissues, hyperinosis, increased coagulability of the blood, increased blood calcium, polycythaemia, dehydration and anoxaemia, bacterial infection of the vessel, tumor cell invasion of the vessel and myocardial insufficiency are considered aetiological factors. It was suggested that, in our opinion, pulmonary diseases such as tuberculosis and silicosis were important aetiological factors. In our series, tracing the thrombosed artery toward the periphery invariably showed that its terminal branches containing thrombi ended as blind pouches. These terminal parts were located either at the centre of the tuberculous or silicotic consolidation or at the wall of the consolidated area.

However, pulmonary disease is not the only determining factor in the production of thrombosis. Of the 100 cases there was definite evidence of parenchymal pulmonary disease in 46, not including those with pulmonary arterial changes associated with cardiovascular disease. In this series of 46 cases, 22 had the thrombus on the right side, 19 bilaterally and 5 on the left side. In the remainder of the 100 cases there was no pulmonary disease. Twenty-seven of these had the thrombus on the right side, 26 bilaterally and one on the left side. This suggests that the right-sided predominance of thrombosis does not depend entirely upon pulmonary disease being more marked on that side but rather upon other factors such as those mentioned above.

The principal clinical features of the 12 cases in our series were increasing dyspnoea, cyanosis, pain in the chest or epigastrium, mental confusion, restlessness, engorgement of the cervical veins, exophthalmos with blurred vision, low pulse pressure with fine thready pulse and

oedema of the ankles in the terminal stages. Marked dyspnoea and cyanosis, as presented by these patients, are rare in uncomplicated pulmonary tuberculosis. Dyspnoea increased steadily and the patients had to be propped up in bed. The cyanosis was most marked about the face, its intensity was comparable to that of *cardiacos negros* of Ayerza's syndrome.

Pain was a prominent symptom in all cases. Not all had the pain in the chest or on the same side as the thrombosis. The pain was deep-seated and vague in its location. The most common area appeared to be the substernal region. In 2 patients the pain began in the epigastrium, later extending into the substernal region.

Restlessness and mental confusion were striking. Most of the patients tossed about in bed. At times they were slightly confused as to time and place. Mental confusion was probably dependent upon cerebral ischaemia. Kampmeier (44), Billings (21) and Schramm (28) attached considerable significance to this symptom.

In 3 cases exophthalmos developed as dyspnoea and cyanosis became severe. The conjunctival vessels became engorged. Blurred vision accompanied exophthalmos which probably resulted from oedema of the retrobulbar areolar tissues and retinal congestion. Low pulse pressure with thin thready pulse was present in most patients. Ankle oedema of varying degree was present in all. It was most marked in the cases with thrombosis of both pulmonary arteries. The liver was palpable when there was bilateral ankle oedema, suggesting pronounced myocardial insufficiency.

In 4 of our series the lungs with the thrombosed pulmonary arteries showed practically no pulmonary tissues because of the extent of the excavation. Yet the occlusion of the vessels supplying these shell-like structures produced most acute dyspnoea, cyanosis and pain in the chest. The possibility of neurogenic factors in the production of such symptoms in association with pulmonary embolism has recently been emphasized by deTakats (59). A similar mechanism may play a part in producing these symptoms in thrombosis.

The clinical significance of the thrombosis of the pulmonary artery in tuberculosis appears to be the close similarity of the symptoms of this condition to those presented by massive spontaneous pneumothorax. Careful examination of the chest both physically and roentgenologically was helpful in differential diagnosis.

## SUMMARY AND CONCLUSIONS

1 Twelve cases of massive thrombosis of the pulmonary artery complicating tuberculosis were studied clinically and at autopsy

2 In 8 the thrombus was in the right pulmonary artery, in 2 in the left artery and in 2 in both arteries

3 Review of 88 reported cases showed a similar preponderance of thrombosis in the right pulmonary artery and definite infrequency of the condition in the left artery

4 Even when there was a thrombus in both arteries, the one in the right artery looked older, suggesting that it originated there

5 It was suggested that the preponderance of thrombosis in the right pulmonary artery and its infrequency in the left artery might be dependent upon the anatomical relation of the arteries to their adjacent structures. On the right side the artery is crossed over by the arch of the aorta and at the hilum it is "squeezed" between the vein and bronchus. On the left side the artery is relatively free

6 The outstanding clinical features are dyspnoea, cyanosis, pain in the chest, restlessness, mental confusion, weak thready pulse, low blood pressure and ankle oedema. This condition simulates spontaneous pneumothorax complicating pulmonary tuberculosis

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## LEUCOCYTE COUNT AND RECOVERY FROM TUBERCULOSIS<sup>1</sup>

Correlation of Neutrophile Polynuclears, Lymphocytes, Monocytes and the Medlar Index with Recovery from Tuberculosis at Different Altitudes above Sea Level

C H BOISSEVAIN AND E N CHAPMAN

In the year 1936 a study was published by Boissevain, Forster and Good (1) on the correlation of blood counts with recovery from tuberculosis. This study covered 1,569 blood counts made on 431 patients at Cragmor Sanatorium, Colorado Springs, Colorado, during the years 1923-1932. The highest correlations,<sup>2</sup> both with condition on leaving the sanatorium and with subsequent condition (1934), were found for the number of neutrophils (- 320 and - 408) and with the Medlar Index (- 400 and - 371). No significant correlation was found with the number of lymphocytes or monocytes. These results were criticized by Smithburn, Sabin and Hummel (2) who considered the total of counts per patient insufficient. The statistical basis for this criticism is not clear, for when each count is correlated with the condition of the patient, as was done in that study, the random variation in each count is compensated by random variations in the opposite direction. This makes the total number of counts and the standard deviation the only measures of accuracy. The total number of patients considered is similarly the measure of the elimination of individual differences between patients.

<sup>1</sup> From the Colorado Foundation for Research in Tuberculosis at Colorado College, Colorado Springs, Colorado

<sup>2</sup> For the benefit of readers not accustomed to the use of the correlation coefficient, this number is used to measure the amount of correlation between two variables. In perfect correlation this coefficient becomes  $\pm 1.00$ . An example of very high positive correlation is, for instance, that between temperature and pulse rate. If the increase in pulse rate were always exactly proportional to the increase in temperature, their correlation coefficient would be  $+1.00$ . The fall in barometric pressure with increasing altitude is an example of a high negative correlation. A correlation of  $\pm .5$  is regarded as of considerable significance whereas a correlation below  $\pm .25$  is considered as of little value though when a large number of data are considered even low correlation coefficients acquire significance. The significance of a correlation coefficient can best be stated in terms of its standard error (given between brackets in the tables). An error equal to the standard error is likely to occur in normal distributions once in three times, one equal to two times the standard error once in twenty five times and one equal to three times the standard error once in four hundred times.

These authors further doubted the reliability of the questionnaire method of ascertaining the condition of the patient after leaving the sanatorium and pointed out that the results from a study on a group of patients, consisting mainly of far advanced cases was not necessarily applicable to less advanced cases. On the basis of their findings in experimental tuberculosis in rabbits, they maintained that the number of monocytes and lymphocytes and their ratio were of greatest value in prognosis, but that no importance could be attached to the number of neutrophils. In this connection it should be pointed out that it is not quite permissible to apply the findings in military tuberculosis in rabbits to chronic pulmonary tuberculosis in man. On the other hand Llaoud and De Crecio (3) have found that, in human lung tuberculosis lymphocytes and monocytes do not reflect significant developments, while a trend of a neutrophile leucocytosis is indicative of the exudative process.

The present study was undertaken in part, to decide the questions raised by Smithburn, Sabin and Hummel. Probably the most complete series of blood counts on tuberculous patients in the country is the one that has been carried on for the past fifteen years at the Metropolitan Life Insurance Company Sanatorium at Mt. McGregor, New York, under the supervision of Dr. E. M. Medlar. Through the kindness of Doctor Ordway, Medical Director of the Sanatorium this series was made available to us for study. The material used consists of 8684 blood counts made on 204 patients during the years 1926 to 1933. The discharge condition on each of these patients was determined by the staff of the sanatorium and recorded at the time of discharge according to the American Sanatorium Association classification, as arrested, apparently arrested, quiescent, improved, unimproved and dead. The subsequent condition was ascertained in 1935 by the excellent "drop" system<sup>2</sup> of the Metropolitan Life Insurance Company and recorded as well, curing or dead. In Craymoor Sanatorium from 1928 to 1932 the classification was not used but instead both discharge and subsequent condition were recorded as cured, arrested, partially improved, stationary, worse or dead. After a comparison of these different standards, we were able to adjust the latter series (to make the correlation coefficients as close as possible) as follows:

<sup>2</sup> The "drop" system is generally preferred to the "questionnaire" method of ascertaining the condition of the patient after leaving the sanatorium. It consists of a series of drops of blood from the patient's finger, which are placed on a card and the color of the drops is noted. The color of the drops is then compared with the color of the drops from a normal person. The color of the drops from a normal person is usually a light pink. The color of the drops from a patient with tuberculosis is usually a darker pink or red. The color of the drops from a patient with tuberculosis is usually a darker pink or red.

by giving it the same notations as those used at Mt McGregor For the Cragmor classifications of subsequent condition, cured, arrested and much improved, the one class "well" was substituted, while improved, stationary and worse became "curing" For comparing the discharge condition it was only necessary to group the two Cragmor classifications stationary and worse together as unimproved This reclassification caused certain changes in the values of the correlation coefficients, without affecting the general picture or the conclusions that could be drawn from them The values of the Cragmor correlation coefficients given in the succeeding tables are, therefore, the new ones and not those of the original publication of Boissevain, Good and Forster

The patients at Cragmor were fairly equally divided over all age-groups, they were mostly referred to Cragmor by other physicians, usually from other states, which perhaps accounts for the large number of far advanced cases in this group The patients at the Metropolitan Life Insurance Company Sanatorium are drawn from the employees of this company, many of them are young women with clerical jobs The periodic health examinations of all employees prevent, to a large extent, the development of far advanced cases of tuberculosis Social and educational standards of both groups were quite similar and treatment in both institutions followed the same general lines Frequent blood counts had been made on all patients at Mt McGregor with an average of 42 per patient These counts and the computation of the Medlar Index had been done under the direction of Doctor Medlar

The frequent blood counts and the follow-up system at the Metropolitan Life Insurance Company Sanatorium are obviously very well fitted to test the validity of the objections made to the Cragmor study The difference in composition of both groups offers an important test of the value of the neutrophiles in prognosis It is always possible to find a prognostic index that fits the series of patients that is being studied The real test comes when this index is applied to a different group of patients The work of Elwood and De Cecio has already confirmed the importance of the neutrophile count on one additional group and the present study offers additional confirmation

A study was recently published by Medlar, Lotka and Spiegelman (4) regarding the value of different indices in tuberculosis with the conclusion that the Medlar Index is the best This study was based on cases *selected* from the same series of blood counts that is the subject of the present study Such a selection seems a dangerous procedure to us for it means

that some cases were eliminated. It is indeed essential in any kind of statistical study that all relevant cases be included. Even random sampling is beset with many pitfalls and is better avoided wherever possible. One of their groups (group 2) consisted of "patients who were on discharge from Mt. McGregor considered pathologically favorable (that is, who had a favorable Medlar Index) and who had remained at work, without relapse, more than five years." The authors then proceed to prove the accuracy of the Medlar Index, obviously, as far as this group is concerned, this result was already implied in the selection of favorable cases only. It is not clear from their study what happened to patients with doubtful or unfavorable index who had remained at work or to those with favorable index who did not recover. A study of groups of such patients would have been of great interest and might have changed the conclusions somewhat. It is the great superiority of the correlation technique that all cases with sufficient data are included.

In the present series all cases were included for which sufficient data were present, as was also done in the Cragmor series. The correlation coefficients were calculated by the computers of the Cowles Commission for Research in Economics, University of Chicago, in a similar manner as described in the paper of Boissevain, Good and Forster. The average of the series of blood counts for each patient was first determined for both the Cragmor and the Mt. McGregor series and the averages correlated with the condition on discharge and the subsequent condition. No correlation coefficients were computed for the number of eosinophiles or basophiles as previous work provides no reason to believe that either is significant.

Both series show a high and approximately equal correlation of subsequent condition and discharge condition with the number of neutrophile polynuclears and the Medlar Index (table 1), but no correlation with the number of lymphocytes. We may consider this as definitely proving the importance of the neutrophile count and Medlar Index in any group of tuberculous patients. The correlation with the number of monocytes is low for the Cragmor series but almost as high as for neutrophiles in the Mt. McGregor series. This may be due to the difference in composition of the two series or to a different technique in classifying the monocytes. A high negative correlation should be shown between monocytes and lymphocytes if the contention of Smithburn, Sabin and Hummel is correct. However, the number of monocytes shows little correlation with the number of lymphocytes in either series, somewhat higher at Cragmor.



TABLE 1  
Comparison of correlation coefficients\*—Mt McGregor data and Cragmor data

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Comparison of correlation coefficients\*—Mt McGregor data and Cragmor data

SIMPLE CORRELATION COEFFICIENTS	1 NEUTROPHILES		2 LYMPHOCYTES		3 MONOCYTES		4 MEDLAR INDEX		5 AGE		6 DISCHARGE CONDITION		7 SUBSEQUENT CONDITION	
	Cragmor	Mt McGregor	Cragmor	Mt McGregor	Cragmor	Mt McGregor	Cragmor	Mt McGregor	Cragmor	Mt McGregor	Cragmor	Mt McGregor	Cragmor	Mt McGregor
1 Neutrophiles	1 0000	1 0000	2709 ( 0454)	— 0847 ( 0695)	5361 ( 0349)	7118 ( 0345)	8427 ( 0142)	8026 ( 0249)			4786 ( 0378)	6575 ( 0397)	4158 ( 0405)	5047 ( 0522)
2 Lymphocytes	1 0000	1 0000	1 0000	1 0000	2701 ( 0454)	1792 ( 0678)	— 2102 ( 0468)	— 6110 ( 0961)			0246 ( 0489)	— 0639 ( 0697)	— 0052 ( 0490)	— 1237 ( 0689)
3 Monocytes					1 0000	1 0000	3972 ( 0412)	5278 ( 0505)			2047 ( 0469)	5852 ( 0460)	1459 ( 0479)	4680 ( 0547)
4 Medlar index							1 0000	1 0000			4812 ( 0376)	5754 ( 0468)	4350 ( 0397)	5106 ( 0518)
5 Age									1 0000	1 0000	0541 ( 0488)	— 0272 ( 0701)	1015 ( 0485)	— 0658 ( 0703)
6 Discharge condition											1 0000	1 0000	7467 ( 0217)	7090 ( 0348)
7 Subsequent condition													1 0000	1 0000

\* Figures between brackets represent standard error

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(270) than at Mt. McGregor (179). The correlation instead of negative is positive in both series. Without attaching too much significance to these low correlations they might be interpreted as indicating a confusion between lymphocytes and monocytes. Of far greater interest is the high correlation between the number of monocytes and number of neutrophils found in both series (Cragmor 536, Mt. McGregor 712). This lends no support to the theory of Maximow and Weidenreich that lymphocytes and monocytes are genetically related and that the latter may develop from the former. It does suggest a close relationship between monocytes and neutrophils, although their similar behavior in tuberculosis does not necessarily imply a genetic relationship. It is also possible that this correlation was caused by counting a certain number of promyelocytes as monocytes; the two types of cells are notoriously difficult to differentiate and the former might well be present in cases with neutrophilic leucocytosis thus causing a parallel increase in the number of monocytes and neutrophils. It would be interesting to know if this correlation between the number of monocytes and neutrophils occurs in other diseases as well as in tuberculosis.

#### MULTIPLE CORRELATION COEFFICIENTS

If we assume that all three types of blood cells, neutrophils, lymphocytes and monocytes, have some value in predicting the outcome of tuberculosis, we can construct a regression equation to compute an index which will show the highest possible correlation with subsequent condition or with discharge condition for the present series. Such a regression equation has the general form  $X = A + B$  (polynuclear neutrophils)  $+ C$  (lymphocytes)  $+ D$  (monocytes). The correlation coefficient of this index  $X$  with the condition of the patient is called the multiple correlation coefficient. They were computed for the Cragmor series as  $r_{d(pml)} = .493$ , meaning that the correlation of the discharge condition of the patient with an index, built up from the figures for neutrophilic polynuclears, monocytes and lymphocytes, equals .493. Similarly we find for subsequent condition  $r_{s(pml)} = .440$ . Comparison with the values given in table 1 shows that these values, which are shown in table 2, are not significantly different from those giving the correlation between neutrophils or the Medlar Index and the condition of the patient. We may conclude that it is impossible to build an index by linear combination of neutrophils, lymphocytes and monocytes, that has a significantly higher correlation than that found for the neutrophils alone.

## TREND INDEX OF NEUTROPHILE POLYNUCLEARS

By calculating the correlation between the average of a long series of blood counts and the condition of the patient, as was done in this study, one important aspect of such a series is neglected. The trend of the blood counts is obviously of the greatest interest. A patient with a certain blood count and a downward trend in the number of neutrophiles

TABLE 2  
Multiple correlation coefficients\*

$r_1(jkl)$	CRAGG	MT MCGREGOR	$r_1(jkl)$	CRAGG	MT MCGREGOR
$r_d(p)$		536 (.050)	$r_m(pmt)$		558 (.048)
$r_s(p,t)$		537 (.050)	$r_s(p,m,t)$		571 (.047)
$r_d(p,m)$		550 (.049)	$r_d(p,t,l)$		536 (.050)
$r_s(p,m)$		528 (.051)	$r_s(p,t,l)$		541 (.050)
$r_d(p,m,l)$	493 (.037)		$r_d(p,m,t,l)$		562 (.048)
$r_s(p,m,l)$	440 (.040)		$r_s(p,m,t,l)$		590 (.046)

p = average number neutrophile polynuclears

m = average number monocytes

l = average number lymphocytes

t = neutrophile trend index

d = discharge condition

s = subsequent condition

\* Figures between brackets represent standard error

has naturally a better prognosis than a patient with the same count and an upward trend.

The use of the slope of a smoothed curve, drawn through the successive counts, at once suggests itself as a measure of the trend. It is, however, in many cases impossible to determine such a slope, as the shape of the curve is often quite irregular, frequent reversals of trend appear typical in many cases of tuberculosis. Another possible measure of trend is

the difference between the average of the first four counts and the average of the last four counts. This eliminates the difficulty arising from an irregular trend but is still open to another objection. A decrease from 12,000 to 6,000 would give a trend index of 6, while one from 6,000 to 3,000 would give an index of 3, although the latter trend is certainly as favorable as the former. We finally used the quotient between the average of the first four counts and the average of the last four counts as index of trend, in the above cases this gives a trend index of 2 in each case. One great difficulty remains: a number of the most favorable cases come to the sanatorium with practically a normal blood count which subsequently remains normal. Despite the highly favorable implication of such a course the trend index is only 1. It is, however, possible to circumvent this difficulty by combining the trend index with the number of neutrophiles in a new index, and then determining the coefficient of multiple correlation. The trend index, thus computed, shows a low but probably significant correlation with the subsequent condition of the patient (table 3), and a still lower but possibly significant correlation with the number of neutrophiles. This led us to consider the possibility of using the trend index only in those patients who had a high neutrophile count. The correlation of trend index with subsequent result in patients with initial counts of 6,000 or more was quite a bit higher than in those with an initial count below 6,000. However, this was not the case if the dividing line came at 5,000 instead of at 6,000, making it probable that the result with the division at 6,000 is due to the accidents of random distribution.

Combination of the trend index with the neutrophile, lymphocyte and monocyte counts gave the highest multiple correlation coefficient (table 2). This correlation (.590) was not as high, however, as the .6575 correlation between the neutrophiles and the discharge condition at Mt. McGregor. It should also be noted that the correlation between discharge condition and subsequent condition was higher in both series .747 and .709 (table 1). In other words, the clinical judgment, based no doubt on the blood-picture among other things, is more accurate than an interpretation based on blood counts alone. While the number of neutrophiles is undoubtedly highly important, the interpretation of trend is perhaps better left to the clinician to be considered in conjunction with other symptoms.

TABLE 3  
*Correlations with trend index\*—McGregor data*

TYPE OF DATA	DISCHARGE CONDITION	SUBSEQUENT CONDITION
Using all available patients	1710 ( 0680)	2859 ( 0643)
Using only those patients where it was considered sufficient data existed for computing the trend	0620 ( 0874)	2398 ( 0827)
Using patients whose average neutrophile count was below 5000	0518 ( 1383)	2773 ( 1280)
Using patients whose average neutrophile count was above 5000	1099 ( 1119)	2784 ( 1044)
Using patients whose initial neutrophile count (av of first 4 counts) was below 5000	1015 ( 1323)	3302 ( 1191)
Using patients whose initial neutrophile count (av of first 4 counts) was above 5000	2112 ( 1111)	3442 ( 1025)
Using patients whose final neutrophile count (av of last 4 counts) was below 5000	— 1953 ( 1242)	— 0771 ( 1283)
Using patients whose final neutrophile count (av of last 4 counts) was above 5000	— 0729 ( 1189)	1828 ( 1155)
Using patients whose initial neutrophile count (av of first 4 counts) was below 5500	0883 ( 1186)	4418 ( 0962)
Using patients whose initial neutrophile count (av of first 4 counts) was above 5500	4490 ( 1031)	3775 ( 1107)
Using patients whose initial neutrophile count (av of first 4 counts) was below 6000	1201 ( 1109)	3876 ( 0956)
Using patients whose initial neutrophile count (av of first 4 counts) was above 6000	5632 ( 0956)	4596 ( 1105)
Using patients whose initial neutrophile count (av of first 4 counts) was below 6500	1472 ( 1055)	4063 ( 0900)
Using patients whose initial neutrophile count (av of first 4 counts) was above 6500	5212 ( 1098)	4469 ( 1207)

\* Figures between brackets represent standard error

## PROGNOSIS AND EFFECT OF ALTITUDE

The curves on chart 1 show the percentage of patients dying or getting well for various gradations in the total neutrophile count, they were "smoothed" to eliminate minor irregularities. The actual number of cases on which the curve is based are given in table 4, which also gives

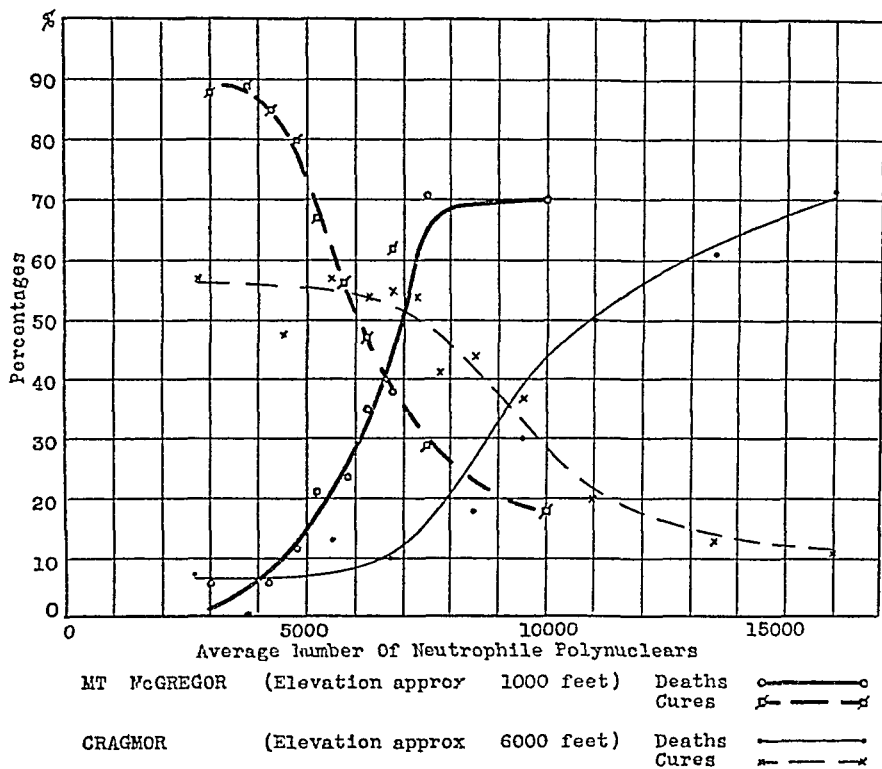


CHART 1 Comparison of percentage deaths and cures at Mt McGregor and at Cragmor for different average neutrophile count

the number of patients still curing (group 2) which are not included in the chart

The curves are surprisingly smooth (an indication that we are dealing with a law of nature) and show an increasing percentage of deaths with increase in neutrophiles and a simultaneous decrease in percentage of cures. Since the number of neutrophiles offers a measure of the condition of the patient, these curves make it possible to compare the end results of similar groups of patients at Mt McGregor and at Cragmor. As

observed before, both groups of patients were treated along the same general lines by competent physicians. Cragmor, near Colorado Springs, however, is situated at 6,400 feet altitude and Mt McGregor at only 1,100 feet. It is well known that blood counts vary with altitude. All those who have studied the subject agree that the percentage of lymphocytes increases and the percentage of neutrophils decreases with an increase of altitude. From the figures given in table 5 it may be seen that the average percentage of neutrophils at an altitude of 6,000 feet is 52.1 per cent, against 60.8 per cent at sea level, while the total number

TABLE 4  
*Number and percentage of patients and their average total neutrophile counts*

NUMBER OF NEUTROPHILES	CRAGMOR						MT MCGREGOR					
	Number			Percentage			Number			Percentage		
	Well	Curing	Dead	Well	Curing	Dead	Well	Curing	Dead	Well	Curing	Dead
1500- 2500	8	5	1	57	36	7	15	1	1	88	6	6
2500- 3500							16	2	0	89	11	0
3500- 4000							28	3	2	85	9	6
4000- 4500	10	10	1	47.5	47.5	5	21	2	3	80	8	12
4500- 5000							16	3	5	67	13	21
5000- 5500	35	18	8	57	30	13	14	5	6	56	20	24
5500- 6000							8	3	6	47	18	35
6000- 6500	20	14	3	54	38	8	8	0	5	62	0	38
6500- 7000	11	7	2	55	35	10	8	0	5	62	0	38
7000- 7500	19	13	3	54	37	9	4	0	10	29	0	71
7500- 8000	11	8	8	41	29.5	29.5						
8000- 9000	24	21	10	44	38	18	3	2	12	18	12	70
9000-10,000	18	16	14	37	33	30						
10,000-12,000	9	14	23	20	30	50						
12,000-15,000	5	10	23	13	26	61						
15,000 and higher	2	3	13	11	17	72						

of leucocytes is somewhat decreased, giving an even greater decline in the total number of neutrophils. This phenomenon is probably connected with the decrease in oxygen pressure, as Balo (5) found the same in animals kept under reduced pressure. In 8 rats kept for three to four days under a pressure of 200 mm. mercury, he found a decrease in the number of leucocytes with relative lymphocytosis. The percentage of neutrophils dropped sharply, in one case to as low as 6 per cent.

We could thus expect to find less favorable results at Cragmor than at Mt McGregor when groups with the same blood count are compared,

but this is not the case. The curves for the percentage of deaths at Mt McGregor and at Cragmor are close together for the low blood counts but begin to separate at 4,500 and then diverge rapidly until at a neutrophile count of 7,000 to 8,000 Mt McGregor shows 71 per cent dead and Cragmor only 18 per cent. The percentage of deaths at Cragmor then rises slowly until it reaches 72 per cent at neutrophile counts of 15,000 to 25,000.

TABLE 5

*Variation of polymorphonuclear and neutrophilic leucocytes with altitude*

AUTHOR	LOCALITY	PERCENT AGE NEUTRO PHILES	TOTAL NUMBER LEUCO CYTES	REMARKS
Staines, James and Rosenberg (6)	Cornell Medical College, sea level	63	7,000	100 male students
Miller (7)	Johns Hopkins Hospital, sea level	64.3	7,200	650 counts, students
Medlar (8)	New York City, sea level	56.6	8,200	247 counts on 18 individuals
Webb and Williams (9)	Harvard University, sea level	59.5		18 students
Average at sea level		60.8	7,467	
Staines, James and Rosenberg (6)	Colorado Springs, 6,000 feet	54.5	7,390	100 male students
Loewy (Stäubli) (10)	St. Moritz, Switzerland, 6,000 feet	52.6	6,675	Visitors to St. Moritz
Loewy (Craandijk) (10)	Davos (Switzerland), 5,000 feet	54.0	6,660	Healthy natives
Webb and Williams (9)	Colorado Springs, 6,000 feet	48.5		18 students
Average at 6,000 feet		52.4	6,908	

The curves giving the percentage of cures show a different behavior. The percentage of cures at Mt McGregor is much larger for the lower neutrophile counts than at Cragmor, almost 90 per cent against 55 per cent, the difference being caused by the much greater percentage in the category "still curing" at Cragmor. The curve for Mt McGregor then drops rapidly while that for Cragmor remains stationary, until at the count of 6,000 the two curves cross, from there on Cragmor shows a higher percentage of cures for all counts.

The differences between the two series could be due to a different



method in classifying the cures but this does not seem likely as the greatest differences occur in the number of deaths. Another explanation might be that the divergence between the two is due to the different composition of the two series. The Mt McGregor series includes more young women, but a study made of the percentages of deaths for women only indicates that they are actually lower than those for the entire group. It is possible that the larger percentage of cures at Mt McGregor in the lower neutrophile counts is due to a greater number of incipient cases there, this could account for at least some of the difference, especially when added to the 20 per cent handicap of Cragmor due to the blood changes at high altitudes. The larger percentage of cures for the higher neutrophile counts at Cragmor might be explained similarly by the presence there of a larger number of "good chronics." Also it is a fact that the unfavorable results in each series are found in the classification with fewest patients, at Cragmor in the cases with low neutrophile counts and at Mt McGregor in the cases with high neutrophile counts. The results might have been somewhat different if more cases had been included in these categories.

However, it is difficult to see how these factors could account for the tremendous difference between 71 per cent deaths in patients running an average count of 7,000 to 8,000 neutrophiles at Mt McGregor and only 18 per cent at Cragmor. It, therefore, seems to the present authors that none of the above explanations is sufficient to account for the differences between the two series, and that the explanation must be sought in the difference in altitude between these two sanatoria, Cragmor at 6,400 feet, Mt McGregor at 11,100 feet. The changes in the blood-picture associated with altitude are in the same direction as those associated with recovery from tuberculosis. It is certainly not unreasonable to suppose that the same factors that influence the blood-picture will also influence the recovery from tuberculosis. It has also been shown by one of us (Chapman) in collaboration with Cowles (11) that there is a high correlation between the white death rate from pulmonary tuberculosis by states in this country and their elevation above sea level. In that study it was impossible to distinguish between the effect of altitude, relative humidity and hours of sunshine, as these three factors are closely related in this country, states with a high elevation above sea level also have low relative humidity and many hours of sunshine. In an effort to distinguish between these factors we have computed an index which measures evaporation from the lungs, assuming that any favorable effect of low relative

humidity on pulmonary tuberculosis is caused by increased evaporation from the lung. Such evaporation depends not only on relative humidity but also on temperature and altitude. The "evaporation index" measuring all these factors showed no correlation with the mortality from pulmonary tuberculosis, making it unlikely that relative humidity is an important factor.

This leaves hours of sunshine and altitude. Similar recomputation to substitute total radiation received per square centimetre for hours of sunshine and oxygen pressure for elevation above sea level, left the correlation coefficients unchanged or increased them. The reputed favorable effect of ultraviolet radiation on surgical tuberculosis is of course a strong argument for considering sunlight as the active factor. The disinfecting action of sunlight may also have epidemiological importance. Some experiments on the influence of radiation on pulmonary tuberculosis in monkeys (unpublished) throw some doubt upon the existence of any favorable effect of sunlight on this disease. Direct sunlight is considered harmful in cases of active pulmonary tuberculosis in man also.

Of the three factors which may exert a favorable effect on pulmonary tuberculosis the oxygen pressure remains to be considered. Oxygen is essential to the tubercle bacillus. It is worthy of note in this connection that all measures of collapse therapy interfere with the oxygen supply of the diseased lung and the usual dyspnoea of pneumothorax patients on exertion makes it very probable that the oxygen supply of the rest of the organism is interfered with. We have already referred to experiments showing that diminished oxygen pressure causes the same changes in the blood picture of experimental animals that are found in recovery from tuberculosis. Also Gutstein (12) found that pneumothorax in dogs caused the same decrease in neutrophiles, which dropped an average of 15 per cent in three animals. This evidence, scanty as it is (and more work is urgently needed on this subject), seems to indicate that the beneficial effect of altitude on tuberculosis is due to a change in the oxygen supply rather than to any of the other factors. Whether the important factor is low oxygen pressure or not, the figures here presented indicate that patients with a neutrophile count of 6,000 or more have a 50 per cent better chance of surviving at a high altitude than at sea level.

## RESULTS

A study has been made on the correlation of blood counts with recovery from tuberculosis on two groups of patients living at different altitudes

Mt McGregor at approximately 1,000 feet elevation and Colorado Springs at approximately 6,000 feet elevation

Both series show an equally high correlation between outcome of tuberculosis and either the total number of neutrophiles or the Medlar Index. Since the figure for total neutrophiles can be computed without the aid of a special calculator it is the method of choice.

The Mt McGregor series also shows a good correlation between outcome and number of monocytes. This is not shown in the Colorado Springs series. The number of monocytes is highly correlated with the number of neutrophiles in both series.

It was shown that it is impossible to obtain by linear combination of values for neutrophiles, lymphocytes and monocytes an index having significantly higher correlation with subsequent condition of the patient than that for neutrophiles alone.

Patients with an average neutrophile count over 6,000 show a much smaller percentage of deaths at an altitude of 6,000 feet than at 1,000 feet elevation.

The authors are deeply indebted to Drs W H Ordway and E M Medlar for putting the Mt McGregor data at their disposal and for their helpful interest, and to the Cowles Commission for Research in Economics, the University of Chicago, for making the statistical computations (involving over 120,000 entries and computations) in their laboratory, and to Mr Forrest Danson of this Commission for valuable advice.

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## LABORATORY PROCEDURES IN INTESTINAL TUBERCULOSIS<sup>1</sup>

ALFRED L. KRUGER AND HARRY J. PERLBERG

Gastroenterology in pulmonary tuberculosis limits itself, from necessity, to the ileocaecal region in attempting to make an early diagnosis of intestinal tuberculosis. Pathologically, the ileum is the site of earliest involvement and this is explained on a two-fold basis—namely, the relative stasis that occurs here and the presence of an abundant lymphatic supply. Primary intestinal tuberculosis is exceedingly rare, especially in the United States, and, when found, is usually due to the bovine bacillus. Secondary intestinal tuberculosis is, on the other hand, the most frequent complication of pulmonary tuberculosis and is found in around 60 to 80 per cent of tuberculous individuals at postmortem. An analysis of 106 consecutive autopsies performed at the Hudson County Tuberculosis Hospital showed the incidence of intestinal involvement to be 61 per cent.

In the past two years, a diagnosis of intestinal tuberculosis was made by means of roentgenological studies on 110 patients with pulmonary tuberculosis. Of this number, 103 had a far advanced pulmonary lesion, 4 were moderately advanced and 3 had a primary lesion.

As emphasized by Cullen (1) and Granet (2), there is a direct relationship between positive sputum and intestinal tuberculosis. Granet, in a study of 740 patients with intestinal tuberculosis, found the sputum to be negative in 4.5 per cent of the cases. In our series, we found 6 per cent of the cases to have a negative sputum (including culture and guinea pig inoculation). Interestingly enough, there were 5 patients in this group who had had an effective collapse for nine months or more when they began to complain of loss of appetite and their weight curve showed a progressive gradual drop. We feel that any patient with a controlled pulmonary lesion who shows these symptoms should be suspected of having an intestinal complication which for some undetermined reason has become manifest. We therefore believe that, although the vast

<sup>1</sup> From the Hudson County Tuberculosis Hospital, Dr. B. S. Pollak, Medical Director, Jersey City, New Jersey.

majority of patients with intestinal tuberculosis will be found to have a positive sputum, the absence of such a finding should not preclude this diagnosis

Contrary to the findings of others, we have found that most of our patients had definite symptoms at the time that the intestinal studies were made. A careful history was taken by one of us (A. L. K.) on all the cases and in only 5 cases (4.5 per cent) was there an absence of symptoms. Forty-two of the patients (38 per cent) had a history of diarrhoea and abdominal cramps of a recurrent nature. Fifty per cent of the cases had a history of anorexia and progressive weight loss, whereas only 6 cases (5.4 per cent) showed a rising weight curve at the time of diagnosis. Nausea and vomiting was found in 26 cases, or 23 per cent. Constipation was noted in 8 per cent.

During the past eighteen months we have made a study of two laboratory procedures, the Woldman phenolphthalein test and examination of stools, to determine whether they were of any help in aiding us to establish a definite diagnosis of intestinal tuberculosis.

#### WOLDMAN'S PHENOLPHTHALEIN TEST

In 1938, Woldman (3) described a simple test for gastrointestinal ulceration which, in his hands, showed a high percentage of positive results. The technique consisted of giving the patient one hour before breakfast 10 cc of a 1 per cent alcoholic solution of phenolphthalein diluted with water to 30 cc. Urine specimens were to be collected at two and four hours after the administration of the solution (a six-hour specimen was to be collected if any cardiac or renal damage was present). The urine specimens were to be examined promptly by the addition of several drops of 10 per cent sodium hydroxide solution and if free phenolphthalein is present a pink or red color will be seen.

The rationale behind the test is that normally 90 per cent of the phenolphthalein is excreted in the urine in a conjugate form which cannot be detected by immediate alkalization of the urine. However, should there be any break in the mucosa of the gastrointestinal tract, greater absorption of the phenolphthalein occurs to the extent that free phenolphthalein is excreted in the urine and this can be detected by alkalization of the urine.

Since Woldman's publication, a number of articles have appeared in the literature. Steigmann and Dyniewicz (4) showed that a minimum of conjugated phenolphthalein must exist in the urine before free phenol-

phthalein could be present and this minimum was 0.03 mg per cent. They concluded that any condition which promoted an increased formation or circulation in the blood of conjugated phenolphthalein will lead to the appearance of free phenolphthalein in the urine. They performed the test on 200 cases, 56 of these having known gastrointestinal lesions, 110 being patients in the hospital with other diseases, and 34 were normal individuals. Of the known gastrointestinal cases, 78.5 per cent had a positive test. A 82.7 per cent positive result was obtained among the 110 other patients and 41 per cent of the normal cases gave a positive test. They concluded that this test could, therefore, not be considered as diagnostic for gastrointestinal ulceration. Kremer, Shore and Wiesel (5) performed the test on 137 patients and found the test to have definite limitations as it was correct in 56 per cent of the cases with gastrointestinal complaints and correct in 79 per cent of cases without gastrointestinal complaints. Suttentfield (6) studied 94 cases and concluded that the test was of no value, 23.3 per cent of their negative cases giving a positive test and 16.7 per cent of their cases with organic gastrointestinal lesions giving a positive result. Similar conclusions were arrived at by Watkin, Kirsch and Albert (7), Slutzky and Wilhelmz (8), LeVine and Kirsner (9), Banks and Barron (10), and Levin and Shushan (11).

The conclusions of the above authors were drawn from observations made chiefly on patients with ulcerations either in the stomach or duodenum. No concerted effort has thus far been made to determine whether or not the test might be of some value in diseases of the colon or terminal ileum.<sup>2</sup> On the assumption that the test might possibly be of some value in intestinal tuberculosis, due to the fact that nearly all such cases have an involvement of the terminal ileum where stasis does occur with consequent greater chance for contact of the phenolphthalein with the areas of ulceration, this test was used on 230 cases of pulmonary tuberculosis.

A gastrointestinal series was done on all 230 cases. The basis for the diagnosis of intestinal tuberculosis was a persistent spasm of the ileocaecal region as defined by Brown and Sampson (12). Of the 110

<sup>2</sup> After we had submitted this paper for publication, an article on *Woldman's Phenolphthalein Test in Intestinal Tuberculosis* by L. E. Siltzbach and H. R. Nayer appeared in the *American Journal of Digestive Diseases*, 1940, 7, 519. The authors performed the test on 206 patients with pulmonary tuberculosis and arrived at the same conclusion as we did, namely, that the test was of no value in determining the presence or absence of tuberculous ulcers in the gastrointestinal tract.

patients with intestinal tuberculosis, 90, or 81.8 per cent, had a positive test, whereas 20, or 18.1 per cent, showed a negative test. Of the 120 cases in whom no intestinal lesions were found, 40, or 33.3 per cent, had a positive test, while 80, or 66.6 per cent, showed a negative test. The percentage of error in both groups was 26 per cent.

The test was performed exactly as described by Woldman. A completely impartial attitude was assumed throughout this study and the result of the test was not allowed to influence the X-ray diagnosis in any case.

The test was used also on 19 patients who came to postmortem. In all these cases, the interval between the date of the test and the date of the autopsy was from two weeks to two months. It was found that the test coincided with the postmortem findings in 14 cases (74 per cent) and failed to agree in 5 cases (26 per cent). Interestingly enough, the percentage of error here (26 per cent) was the same as the percentage of error in the above group of 230 cases.

#### STOOL EXAMINATION

Every patient with pulmonary tuberculosis with symptoms referable to his gastrointestinal tract has three stool examinations on consecutive days after being on a meat-free and fish-free diet for three days. This always precedes the roentgenological study of the intestinal tract. The reason for this is that the roentgenological signs of intestinal tuberculosis are merely indirect spastic phenomena encountered in any ulcerative lesion and all efforts must be made to rule out other possibilities (that is, amoebiasis) before making a diagnosis of intestinal tuberculosis. A total of 474 stool examinations were carefully done on 158 patients, 79 of these patients were found to have roentgenological evidence of intestinal tuberculosis, while the other 79 were found to be free of intestinal disease. Occult blood (benzidine test) was found in the intestinal cases almost twice as frequently as in the negative cases, 60 per cent of the positive cases and 35 per cent of the negative cases giving a positive test. Cellular exudates (pus cells, lymphocytes) on the other hand were found with almost equal frequency in both groups (56 per cent of the positive cases and 59 per cent of the negative cases). No attempt was made to grade the number of cells found, an occasional pus cell in a stool examination was called positive just as were those containing a larger number. Berkovitz (13), from a careful study of cellular exudates of 1,123 individuals, concluded that where there was a diseased bowel cellular exudates would be found in the stools and, conversely, no cells would be found in





## INFLUENCE OF POSTURE ON THE INTRAPLEURAL PRESSURE IN ARTIFICIAL PNEUMOTHORAX<sup>1</sup>

SAMUEL COHEN

The intrapleural pressure under ordinary conditions is always sub-atmospheric or negative. This negative pressure is greater during inspiration and reduced during expiration. During quiet inspiration in humans it amounts to about  $-6.0$  cm. of water and during expiration it is reduced to about  $-2.5$  cm. of water, in the midposition it is approximately  $4.5$  cm. When these respiratory movements are forced the intrapleural pressure, of course, may be tremendously increased or decreased in the respective phase of respiration. These fluctuations in pressure exert, as is well known, an influence upon other structures in the thorax, particularly upon the filling and emptying of the thin-walled veins.

Carson (1820) (1) was apparently the first to measure the "resilient property" of the lungs in animals by connecting a water manometer to the windpipe and observing the pressure change after a bilateral open pneumothorax had been induced. Powell (1868) (2) was the first to record positive intrapleural pressure in a valvular pneumothorax ("the air pressure was found to be equal to four inches of water"). This was done on the cadaver of a patient who died of pulmonary tuberculosis. The first successful effort to measure the intrapleural tension in normal living persons was evidently made by Aron (1891) (3). Readings (a glycerine manometer connected with a syphon drain was used) were taken during both phases of respiration (the time interval in seconds of inspiration and expiration was also noted) and in the lying and sitting positions. In recent years, Christie and McIntosh (1934) (4) particularly have emphasized the variations in distensibility of the lungs with changes in posture. They noted that the change from the recumbent to the sitting position resulted in a decrease of the intrapleural pressure by about  $2.5$  cm. of water. The change was accompanied by an increase of several hundred cubic centimetres of air in the lungs. Prinzmetal and Kountz (1934) (5) took the intrapleural pressures in both the recumbent

<sup>1</sup> From the Hudson County Tuberculosis Hospital, Dr. B. S. Pollak, Medical Director, Jersey City, New Jersey.

and upright positions in 13 individuals, 7 of whom were orthopnoeic and 6 were not. In all cases the intrapleural pressure was less negative or more positive in the former position. The shift was greater in patients with orthopnoea than in the control group.

#### PRESENT STUDY

*Material* This study was undertaken with the purpose of determining the influence of posture on the intrapleural pressure of patients receiving artificial pneumothorax. One hundred and ten cases who were receiving this therapy for pulmonary tuberculosis were studied. Their ages ranged from thirteen to forty-nine years. Ninety-eight had a unilateral and 12 a bilateral pneumothorax. The duration of collapse therapy varied from two weeks to thirty-two months and the degree of pulmonary compression from about 15 to 90 per cent.

*Procedure* With the needle in the pleural cavity at the same site (in almost all of these cases the site was the third anterior interspace in the anterior or midaxillary line), readings were recorded with the patients in the following positions: flat on back or supine, lateral recumbent (pneumothorax side up), sitting. The patient was instructed to breathe naturally and the accepted reading was reached when three consecutive readings at the end of inspiration and expiration were the same or as nearly the same as could be reasonably expected. The Bethune pneumothorax apparatus was used and the intrapleural findings expressed in centimetres of water (the change was measured in only one arm of the manometer). A kymograph attached to the pneumothorax machine can be utilized to obtain permanent visual records (figure 1). The arrangement is simple and applicable for teaching purposes.

#### RESULTS AND CONCLUSIONS

1 The intrapleural pressures were consistently found to be

- (a) Most subatmospheric in the lateral recumbent position
- (b) Less subatmospheric in the sitting position
- (c) Least subatmospheric or most positive in the supine position

2 The intrapleural variations were as follows

- (a) Differences between readings in lateral recumbent and supine posture

	<i>At end of inspiration in cm. of water</i>	<i>At end of expiration in cm. of water</i>
Minimum difference	0	0.5
Maximum difference	9.0	12.0
Average difference	2.7	4.3

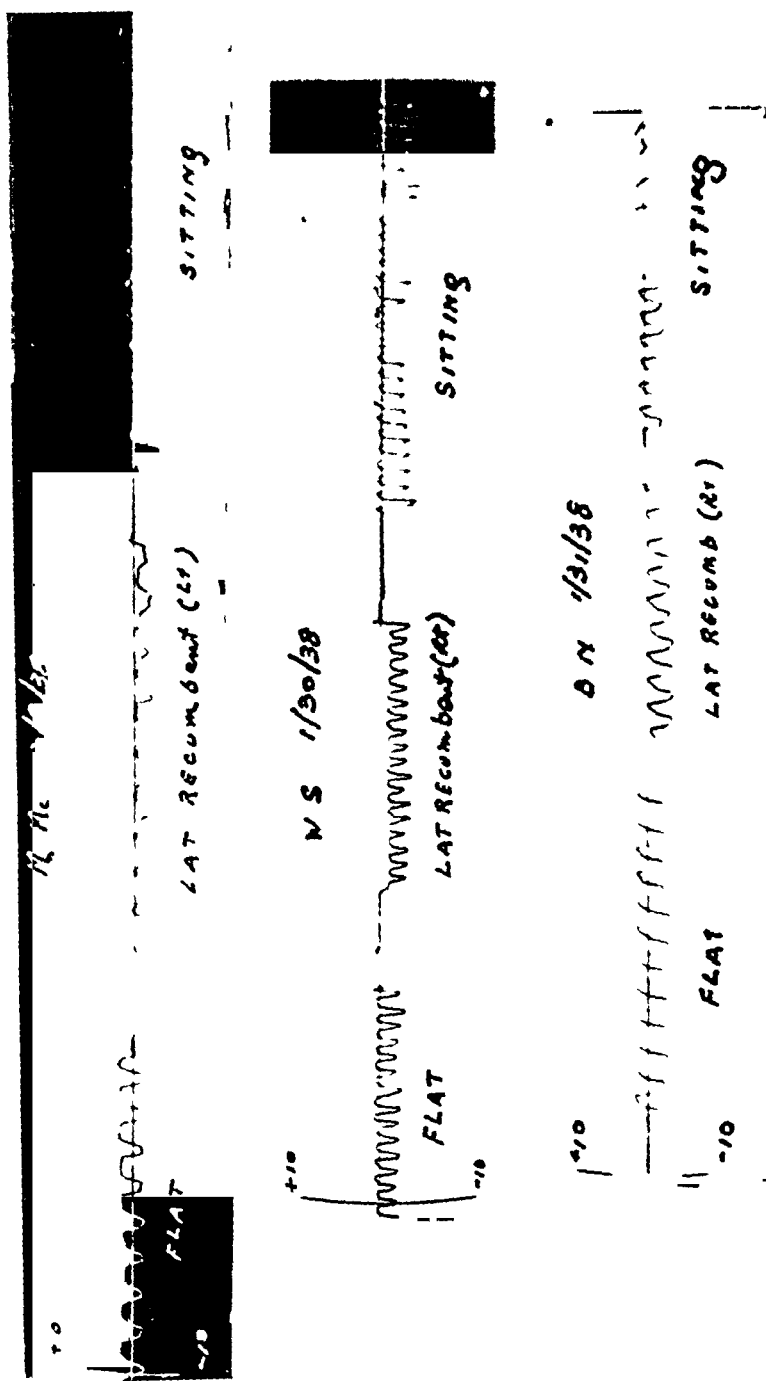


Fig-1

## (b) Differences between readings in lateral recumbent and sitting-up posture

	At end of inspiration in cm. of water	At end of expiration in cm. of water
Minimum difference	0	0
Maximum difference	7.0	10.0
Average difference	1.5	2.9

## (c) Differences between readings in sitting-up and supine posture

	At end of inspiration in cm. of water	At end of expiration in cm. of water
Minimum difference	0	0
Maximum difference	7.0	10.0
Average difference	1.5	1.8

It is noted that in all three instances, the greatest average variation was at the end of expiration.

3 In the 12 cases with bilateral pneumothorax, simultaneous pressure readings were taken on both sides. As mentioned above, the intrapleural pressure is most subatmospheric in the lateral recumbent position. This is true on the pneumothorax side that is uppermost. The simultaneous reading on the dependent pneumothorax side definitely becomes more positive due to diminished respiratory movement on this side and the displacement of the mediastinum toward it.

4 In a recent excellent article, McMichael and McGibbon (1939) (6) reported on the postural changes in pulmonary volume. They observed the following physiological changes in the supine position which undoubtedly explain why intrapleural pressures are least subatmospheric in this position: (a) a decrease of total lung volume (the average reduction was 340 cc. in the group of 25 patients studied)—this is believed due to increased congestion of the pulmonary vessels in the supine position, (b) a decrease in functional residual air (average 780 cc.)—this is caused by the upward displacement of the diaphragm by the abdominal organs which reduces the air volume in the lungs, (c) a decrease in residual air (average 150 cc.), (d) a decrease in vital capacity (average 190 cc.).

## SUMMARY

The intrapleural pressure under ordinary circumstances is a subatmospheric pressure.

A study of 112 cases of artificial pneumothorax (12 of which were bilateral) has been undertaken in order to determine the fluctuations in intrapleural pressure during quiet respiration with changes in posture of

the patient Readings were obtained with the patient in the following positions (a) supine, (b) lateral recumbent, and (c) sitting The findings have been presented briefly The attachment of a kymograph to the pneumothorax apparatus makes available permanent registration of the pressure readings

Physiological changes in pulmonary volume dependent on postural changes are associated with variations in the intrapleural pressure

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# CHEMOTHERAPY OF EXPERIMENTAL TUBERCULOSIS<sup>1</sup>

H HARRIS PERLMAN, HERMAN BROWN AND GEORGE W RAIZISS

With the assistance of Miss Anna Rule

For many years men have been seeking to discover a chemotherapeutic agent destructive of the tubercle bacillus *in vivo*. The resulting voluminous literature is proof of the enthusiastic endeavors of the research workers in this field. However, it is not the purpose of this paper to review in any great detail that literature, especially since a brief review of such contributions is already available in the excellent treatise of Wells and Long (1), rather it is to present certain researches that have been undertaken recently in the hope of adding to the work accomplished previously in that field.

## REVIEW OF THE LITERATURE

*Volatile oils (etheral oils)* Baldwin, Petroff and Gardner (2) observed that the vapors of volatile oils, such as peppermint, clove, eucalyptus, restrain the growth of cultures of tubercle bacilli, but they presented no data of animal experiments.

Cinnamic acid, a constituent of balsam of peru, has been studied by several investigators. As early as 1893 (3) Landerer injected intravenously an alkaline 5 per cent cinnamylic acid emulsion (with egg yolk) in 18 individuals afflicted with internal (visceral) tuberculosis. Somewhat earlier Landerer had used balsam of peru but he found his results with cinnamic acid were more striking. Of these, he said, "In the treatment of surgical cases of tuberculosis cinnamylic acid is in its effect equal to iodoform. While admitting the fact that many physicians declare intravenous injection to cinnamylic acid emulsion as a dangerous process there are no unpleasantness nor any threatening conditions in applying this form of treatment provided the doses administered are kept within certain limits." Landerer concluded by expressing his faith in this form of medication and hoping that it would find wide application. Later he employed sodium cinnamate or ketol, for which he claimed better therapeutic results than for the emulsion. Other advantages of the

<sup>1</sup> From the Research Institute of Cutaneous Medicine, Philadelphia, Pennsylvania

sodium salt were its solubility to the extent of 5 per cent, its nontoxicity, its ease of sterilization and its availability in pure form, yet, after many trials, sodium cinnamate, too, was discarded as unsatisfactory, because it proved therapeutically inefficient

Jacobson (4) studied a derivative of cinnamic acid which has a cinnamic acid radical and at the same time possesses an alcoholic action, namely, cinnamic ether of ethyl alcohol or ethyl cinnamic ether. Jacobson carried out his researches both *in vitro* and *in vivo*. *In vitro* he studied the development of Koch's bacillus on glycerine-potato medium to which he added ethyl cinnamic ether. His conclusion was, after deductions from weight experiments, that 0.001 mg. of ethyl cinnamic ether hindered the development of 0.002 mg. of culture of Koch bacillus. *In vivo*, Jacobson studied the thermic reaction brought about by tuberculin upon the tuberculous organisms. Using either method, he proved that the thermic action provoked in tuberculous guinea pigs by the injection of pure tuberculin is more intense and of longer duration than the thermic reaction produced in like guinea pigs by a like quantity of tuberculin mixed with ethyl cinnamic ether. He found also that ethyl cinnamic ether, injected subcutaneously into tuberculous guinea pigs, brought about a passing leucocytosis, the same quantities of ethyl-cinnamic ether injected into nontuberculous guinea pigs caused no leucocytic reaction.

In a series of notes addressed to the Société de Biologie, Jacobson (5) indicated the reasons which led him to try benzyl-cinnamic ether. With it he obtained favorable results in the treatment of cutaneous tuberculosis which were confirmed by Darier, Jean-Selme, Mitchnick, Froitsard and by others at three congresses of dermatology held in the French language (1922, Paris, 1924, Strasbourg, 1926, Brussels), particularly by Vignes and Fournies. Benzyl-cinnamic ether is said to have been used efficaciously in the treatment of tuberculous lymph nodes, genital tuberculosis, tuberculosis of the mucous membrane, tuberculosis of the larynx and also in the treatment of tuberculous cysts. However, in the treatment of pulmonary tuberculosis, Jacobson admitted that his studies and observations were of short duration, although he spoke highly in favor of the treatment.

Corper *et al* (6) elaborated on Jacobson's studies with sodium-cinnamate. Geller (6) from preliminary studies felt it possessed possibilities as a tuberculocide because of its low toxicity. He found that repurified sodium cinnamate in concentrations of 2 per cent has no tuberculocidal action within three days, but is distinctly inhibitory to the human

tubercle bacillus in 5 per cent glycerine-agar in a concentration of 0.05 per cent, while in rabbit-blood medium, both fresh and inspissated, it is inhibitory only in a concentration of about 0.2 per cent. However, he found that sodium cinnamate cannot be used as an inhibitory agent in tuberculosis over a prolonged period of time because of its haemolytic action.

#### GENERAL PROCEDURE

In line with the foregoing researches, in the present studies an attempt was made to determine the effect, in guinea pigs infected with a virulent strain of bovine tubercle bacilli (Ravenel), of certain chemical compounds, namely, thymol, menthol, cinnamic aldehyde and eucalyptol which represent the solid portions of volatile (aromatic) oils known chemically as stearoptens. They were employed either alone or injected in physical combination, dissolved in sterile peanut oil in strengths of 2.5 to 10 per cent. Similar studies were carried out with alkyl phenols and their halogenated derivatives, the latter group of compounds including monochloro-iso-amyl-thymol, monobromo (1-ethyl-propyl-m-cresol) 1-ethyl-propyl-beta-naphthol. Lastly, four amino-acids, namely, cystine, asparagin, glycine and alanine, were administered subcutaneously to tuberculous guinea pigs in 10 per cent strength in sterile distilled water in order to determine their effect in preventing loss in body-weight.

The series of investigations were carried out from the following standpoints of inquiry: (1) The effect of the therapeutic remedy upon nutrition, as gauged by gain or loss in weight in the animals studied. It is to be noted as a precaution against miscalculation that the loss or gain in weight of guinea pigs infected with a virulent strain of tubercle bacilli represents a combination of two factors, namely, the age of the animal and the effect of the infection. Accordingly, since most of the guinea pigs in the present studies were quite young, it is to be understood that their natural growth may have had more effect than the tuberculous infection, and thus may account for a net gain in weight, which otherwise would not have occurred.

(2) Evidence of infection with tuberculosis as noted upon weekly examination, by (a) a gradual increase in the size of the right and left chains of inguinal lymph nodes, (b) by observing the gross lesions characteristic of tuberculous infection in the lymphatic structures and other organs, such as the spleen, liver, lungs, pleural and peritoneal cavities, at the time of autopsy.



(3) Longevity of treated animals compared to that of untreated but similarly infected controls

(4) Microscopical evidence by identification of tubercle bacilli in stained smears of various organs infected with tuberculosis Further, an attempt was made to evaluate the severity or mildness of the infection by observing the numbers of tubercle bacilli found in the smears

#### EFFECT OF THYMOL, MENTHOL, AND THYMOL AND MENTHOL COMBINED

Four series of 4 guinea pigs each were inoculated subcutaneously in the left groin with 0.2 cc of saline containing 0.00005 mg of tubercle bacillus (Ravenel) Three days later the first series of animals received intramuscularly, and thereafter at five day intervals, alternately in the right and left thighs, 5 per cent thymol in peanut oil in doses of 0.4 cc per kilogram weight, the second series of animals, 5 per cent menthol in peanut oil in similar dosage, the third series, 5 per cent thymol and 5 per cent menthol in dosage of 0.2 cc per kilogram body weight The fourth or control group received peanut oil without any medication in dosage of 0.4 cc per kilogram of body weight All animals were weighed once every five days, at which time they were examined to determine the size of the inguinal lymph nodes A rest period of two weeks' duration was instituted after the fourth injection of both the medicated and nonmedicated oil because of the induration of the thigh muscles that resulted from repeated injections

As a result of the foregoing procedure, all treated animals lost weight, the loss was only slightly less for the treated animals than for the untreated animals, the average loss for the three treated groups being 62.3 g, as compared to 71 g for the control animals

The three groups of treated animals lived ten days longer (average ninety-two days) than the control groups (average eighty-two days)

Milder infections occurred in the 5 per cent thymol and the combined 5 per cent thymol and 5 per cent menthol groups than in the animals of the 5 per cent menthol and the control groups

Accordingly, it is inferred that 5 per cent thymol or a combination of 5 per cent thymol and 5 per cent menthol was responsible for the milder types of infection in the animals so treated

#### EFFECT OF THYMOL AND MENTHOL COMBINED AND OF CINNAMIC ALDEHYDE AND EUCALYPTOL

The encouraging results with 5 per cent thymol and 5 per cent menthol in the previous study suggested the further use of both these compounds

in combination, but in 2.5 per cent strength. Accordingly, three series of 4 guinea pigs each were treated in the manner already described, the first series with 2.5 per cent thymol and 2.5 per cent menthol, the second series with 5 per cent cinnamic aldehyde, the third series with 5 per cent eucalyptol. Again, the compounds were dissolved in peanut oil and administered in dose of 0.4 cc per kilogram of body weight.

Two treated groups of guinea pigs gained weight, the greater gain being made by the 5 per cent eucalyptol group, while one group lost weight.

There was no appreciable difference in the survival time of the treated animals, as compared to that of the controls. The longest duration of life was found in the 5 per cent cinnamic aldehyde group, but the animals in that group lived only seven days longer than the controls.

The most encouraging results, in order of importance as determined by the examination of smears for tubercle bacilli, were found in the following groups: (1) 5 per cent eucalyptol, (2) 2.5 per cent thymol and 2.5 per cent menthol, (3) 5 per cent cinnamic aldehyde. Accordingly, from the foregoing study it is inferred that 2.5 per cent thymol and 2.5 per cent menthol, also 5 per cent cinnamic aldehyde and particularly 5 per cent eucalyptol, probably play some part in rendering infection with tubercle bacilli milder in guinea pigs.

#### EFFECTS OF COMPOUNDS SINGLY AND COMBINED IN 10 PER CENT STRENGTH

This experiment was in part a repetition of the first study, except that the thymol and menthol were doubled to 10 per cent. The procedure was also followed with thymol and menthol combined in 10 per cent strength. Because of the encouraging results observed with eucalyptol, that compound was also used in 10 per cent alone in two separate experiments and in combination with 10 per cent menthol and in combination with 10 per cent thymol.

Seven series of 5 guinea pigs each were inoculated and treated according to the uniform procedure of these experiments.

Treatment and survival times were as follows:

	days
Group I 10 per cent eucalyptol	53
Group II 10 per cent thymol	37
Group III 10 per cent menthol	40
Group IV 10 per cent eucalyptol and 10 per cent thymol	48
Group V 10 per cent eucalyptol and 10 per cent menthol	59
Group VI 10 per cent thymol and 10 per cent menthol	48
Group VII Controls	23

## Two groups of animals, both treated, gained weight

10 per cent eucalyptol and 10 per cent thymol  
10 per cent eucalyptol

groups  
29  
8

An interesting observation was afforded by a study of the size of the inguinal lymph nodes. In animals treated with 10 per cent eucalyptol, 10 per cent thymol or 10 per cent menthol, the lymph nodes, both at the site of infection and upon the opposite side, either remained normal or were only slightly enlarged. Likewise, animals treated with combinations showed only slight enlargement of the nodes. In contrast, in the majority of the controls the nodes were very much enlarged.

All organs showed evidence of tuberculosis. The lesions consisted of definite enlargement of the spleen, although in a few instances among the 10 per cent eucalyptol-treated group, the spleens appeared normal upon gross examination. Necrotic lesions were found in most of the spleens and livers. The lungs of one of the 10 per cent menthol-treated animals showed abscess formation but among the controls were noted pneumonia and pleurisy.

In smears from the organs, the most numerous negative findings were found in the 10 per cent thymol group (16 negative, 4 positive). The next largest number of negative smears was among the 10 per cent eucalyptol group (8 negative, 12 positive), and the same for the 10 per cent menthol group.

Because of the significant increase in longevity shown by the 10 per cent eucalyptol group, and the combined 10 per cent eucalyptol and 10 per cent menthol group, it seemed worth while to continue experiments with these medications. Accordingly, two series of 6 guinea pigs each were inoculated and treated according to the procedure already detailed: the first series with 10 per cent eucalyptol in peanut oil, the second series with 10 per cent eucalyptol and 10 per cent menthol in the same medium in a dosage of 100 mg per kilo of body weight. Together with these a series of 13 controls was employed.

Generally, the results of these two series were far less striking than those of the preceding series.

All animals gained weight, the 10 per cent eucalyptol treated, 8 g, the 10 per cent eucalyptol and 10 per cent menthol treated, 1 g. However, the controls gained 13 g.

All animals, both treated and untreated, showed slightly enlarged inguinal lymph nodes. Examination of the organs of the treated groups

showed no demonstrable differences from those of the controls, all gave gross evidence of tuberculosis. Smears showed no appreciable differences between treated and untreated animals.

From the foregoing results it is inferred that certain chemical compounds administered to guinea pigs, either alone or in combination, exert some influence upon the severity of the infection so that it is rendered milder in treated than in untreated groups of animals similarly infected.

#### EFFICIENCY OF VARIOUS ALKYL PHENOLS AND THEIR HALOGENATED DERIVATIVES UPON EXPERIMENTAL TUBERCULOSIS IN GUINEA PIGS

Nine series of guinea pigs were inoculated and treated in the usual manner of these experiments. The compounds administered were prepared in 5 per cent solutions of sterile olive oil, and each was given in dosage of 10 cc per kilogram of weight. The following compounds were given to infected guinea pigs.

CHEMICAL COMPOUNDS	NUMBER OF GUINEA PIGS
Part I	
Monochloro iso-amyl thymol	5
Monobromo (1-ethyl propyl) m-cresol	5
Iso amyl thymol	5
Menthyl thymol	5
Menthyl thymol	5
Controls	7
Part II	
Monochloro (1-ethyl propyl) p-cresol	4
(1-ethyl propyl) beta naphthol	4
Controls	3

All treated animals lost weight. The greatest loss was incurred by the monochloro-iso-amyl-thymol treated group (75 g), the smallest loss occurred in the iso-amyl-thymol group (6 g). The control group in part II gained 27 g.

As compared with longevity in the control group of guinea pigs, no startling difference was observed in any of the groups of treated pigs. The mean duration of life for the control group of animals in part I was thirty-one days, while the mean longevity of the treated groups of guinea pigs varied from twenty-nine to thirty-three days. All treated and

untreated animals died from tuberculosis. In part II, the mean duration of life was nineteen days. One group of treated guinea pigs lived 20 days and another twenty-three days. All animals in the treated and control groups died.

The lymph nodes of all treated animals, as well as those of the control group, showed only slight enlargement. All animals showed unmistakable signs of tuberculosis. The spleens were enlarged and, for the most part, spotted. The livers and lungs of all animals were spotted with tuberculous lesions. Smears of the spleen, liver and lung showed tubercle bacilli.

Certain alkyl phenols and their halogenated derivatives failed to prevent loss of weight, to increase longevity or prevent the spread of disease in tuberculous guinea pigs.

#### THE RESPONSE OF WEIGHT LOSS TO CERTAIN AMINO-ACIDS IN EXPERIMENTAL TUBERCULOSIS

The object of this study was to determine whether amino-acids had any effect in preventing loss of weight, such as is incident to the progress of tuberculous infection in guinea pigs. The same procedure for studying the effect of the amino-acids upon tuberculosis in guinea pigs was employed in this study as was carried out with the various agents in the foregoing investigation.

Four series of 3 guinea pigs each received an aqueous sterile 10 per cent solution of the following amino-acids: cystine, asparagin, glycine and alanine. A fifth series of 13 guinea pigs served as controls.

With the exception of cystine, the subcutaneous injection of certain amino-acids, namely, asparagin, glycine, and alanine, in 10 per cent aqueous solution, repeatedly administered to guinea pigs infected with tubercle bacilli, failed to prevent loss in weight to any appreciable degree.

There was no marked difference in the longevity of guinea pigs treated with the amino-acids as compared with that of the control group.

The acids showed no demonstrable effect on the severity of tuberculous infection in guinea pigs. At autopsy all animals had characteristic lesions of tuberculosis, confirmed by identifying the tubercle bacillus in smears from various organs.

#### SUMMARY

1 The subcutaneous administration of 5 per cent thymol, menthol, eucalyptol and cinnamic aldehyde to guinea pigs, infected with a virulent

strain of bovine tubercle bacilli (Ravenel), rendered infection milder as compared to that in similarly infected untreated animals. The longevity of the treated animals was appreciably increased as compared to that of the control groups of pigs, and there was in many instances a failure to recover tubercle bacilli by an examination of stained smears from the various organs.

2 Encouraging but less striking results were obtained with guinea pigs when thymol and menthol were administered separately in 10 per cent solutions.

3 Moderate to severe tuberculosis was observed in guinea pigs treated with 10 per cent eucalyptol, 10 per cent each of eucalyptol and menthol combined, 10 per cent each of thymol and menthol combined, and 10 per cent each of eucalyptol and thymol combined. In these experiments it was found that longevity was twice, and often two and a half times, as long as that of control groups.

4 The alkyl phenols and their halogenated derivatives had no effect in mitigating the infection, in preventing a loss in weight or in increasing longevity, as compared to that of untreated infected animals. On the contrary, some of the severest lesions were found in the treated animals of this group.

5 The amino-acids, cystine, asparagin, glycine and alanine, failed to prevent loss of weight, to increase longevity, and to modify the course of the infection in guinea pigs injected with a virulent strain of tubercle bacilli.

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# SPONTANEOUS CLOSURE OF TUBERCULOUS CAVITIES<sup>1,2</sup>

## A Roentgenological Study

E. ROBERT WIESE

The work here presented was undertaken to determine, as nearly as possible, the incidence of spontaneous closure of tuberculous cavities of the lungs in patients in White Haven Sanatorium

We have made extensive study of the reports and of the X-ray films of 1,000 patients. These 1,000 cases comprised the following

Pulmonary tuberculosis with cavitation	597
Pulmonary tuberculosis without cavitation	129
Normal lungs and healed lesions	99
Anthracosilicosis	61
Anthracosilicosis and tuberculosis	88
Other conditions	
Pleuritis, bronchiectasis, abscess, neoplasms, cysts of the lungs, chronic congestion, Hodgkins disease	26

From the 597 cases of pulmonary tuberculosis with cavitation the following were deducted because they were not suitable for our study

165 patients who died while in the Sanatorium
184 patients subjected to some form of collapse therapy
123 cases having but one film and hopeless cases

This left 125 cases of pulmonary tuberculosis with cavitation that were suitable for our study

These 125 were not selected, but were for the most part at least rejected cases, as they had been considered not suitable for collapse therapy. Upon study we found among them 20 instances where closure took place spontaneously with no other treatment than that of strict bed-rest. For the purposes of this paper a cavity was considered closed when the outlines of the walls or the area of rarefaction could no longer be seen roentgenologically and marked improvement in the condition of the patient was noted clinically. While these patients were never considered

<sup>1</sup> From the White Haven Sanatorium, White Haven, Pennsylvania

<sup>2</sup> Summary of a paper read before the Laennec Society of Philadelphia, April 9, 1940

hopeless, none was ever looked upon as promising of good results. The essential features may be summed up as in tables 1 and 2.

As a rule the cavities were regular in outline, there were but 3 exceptions. In all instances the walls were thin. The method of closure varied, it was quite the usual thing to see them gradually becoming smaller when successive films were compared, until one could see only a small fibrotic deposit or several strands of fibrotic tissue, not infrequently stellate in outline, in place of the former cavity. In one instance nothing remained visible to indicate the site of the lesion. In another case the

TABLE 1

SEX	NUMBER	OLDEST	YOUNG EST	SPUTUM				CAVITY	
				On admission		On discharge			
				Positive	Nega tive	Positive	Nega tive	Right	Left
Males	10	48	20	10		3	7	8	2
Females	10	33	20	10			10	2	8

TABLE 2

SIZE	NUMBER	CLOSURE TIME	CONDITION OF PATIENT MARCH 1940	CAVITY HAS BEEN CLOSED MARCH, 1940
		<i>months</i>		
Up to 2 cm	4	2 to 23	4 living and well	8 months to 6 years 10 months
2 to 3 cm	5	3 to 22	1 unknown 4 living and well	1 year to 3 years 9 months
3 to 4 cm	7	3 to 67	7 living and well	6 months to 6 years 5 months
Cavity nests	4	6 to 16	4 living and well	2 years 3 months to 3 years 9 months

area occupied by the cavity became dense and resembled ground glass, an appearance indicative of atelectasis, this gradually diminished in size and eventually left behind a scar.

The above is but a summary of the cases in which cavities closed spontaneously on bed-rest only. Under no circumstances do we wish to give the impression that 16 per cent of all cavities will close spontaneously on bed-rest. Our search however has shown that in this particular group 16 per cent of our cavity cases closed spontaneously where collapse therapy was not employed in patients who were not hopelessly ill.



# PRESENT STATUS OF THE TUBERCULIN PATCH TEST<sup>1</sup> 2

CAMILLE KERESZTURI

The tuberculin test is one of the most important adjuncts in the control of tuberculosis. Best known among the tuberculin tests done by injection are the subcutaneous test of Koch, the percutaneous test of Pirquet and the intracutaneous test of Mantoux. The last has stood best the test of time.

In spite of the satisfactory character of the Mantoux test, there has been a continuous search for a tuberculin test which eliminates the process of injection. In other words, a test has been sought which requires mere contact between the patient's skin and Old Tuberculin. Among the contact tests used in Europe the innunction method of Moro and the plaster ointment test of Malmberg and Fromm are the best known. Both are regarded as inferior to the Mantoux or Pirquet tests.

In the United States the patch tuberculin test of Vollmer, first described in 1937, has aroused considerable interest. The present study and review of reported findings was undertaken in response to this interest and with a view to assessing the value of the simplified contact test.

## TECHNIQUE OF THE PATCH TEST OF VOLLMER

"Thin filter paper is saturated with tuberculin, produced on a synthetic medium, dried, cut into squares of 1 x 1 cm. and placed on adhesive tape 1 x 3 inches in size. Each strip of tape contains two tuberculin squares placed on each side of a control square, the latter consisting of filter paper saturated with glycerin broth. The dried tuberculin contained in the filter paper must be protected from excessive moisture before use. Through the natural moisture of the skin (*perspiratio insensibilis*) the tuberculin is dissolved and absorbed sufficiently to render reliable cutaneous reaction."

<sup>1</sup> From the New York Institute for the Education of the Blind, Department of Pediatrics, Columbia University, New York City.

<sup>2</sup> This study was made possible through the interested cooperation of Dr. William Barclay Parsons, one of the trustees of the New York Institute for the Education of the Blind, of Dr. Merle E. Trampton, the Principal, and of Mrs. K. D. Longsdorf, R.N., the nurse of the school. Dr. Ashley Weech from Babies Hospital was kind enough to read the manuscript and give helpful criticism and suggestions.

Doctor Vollmer and the Lederle Laboratories are recommending the following method for making the patch test

"An area of skin over the sternum, along the upper spine, or on the inner side of the forearm, is thoroughly cleansed and defatted with acetone, (a small pledget of fresh cotton for each patient) Hairy areas should be avoided In the case of children the sternum is better In the case of infants it may be preferable (in order to avoid accidental or deliberate premature removal of the adhesive tape) to place the test on the back, along the upper spine The entire strip of adhesive, after the removal of the crinolin, is applied carefully to the cleansed area under pressure with the warm palm of the hand Care should be taken to keep the paper squares near the central line of the adhesive tape If they become misplaced toward the margin of the tape, they may not be properly sealed in

"Leave the tape holding the patches in contact undisturbed, for forty-eight hours, then remove the tape Make reading of the test forty-eight hours after removal of the tape

"The removal of the tape, even if replaced at once, during the forty-eight hour period of contact, may result in fewer positive reactions Bathing or wetting of the affected area should be avoided during the forty-eight hour period

"While some positive reactions may be read immediately after the removal of the tape, it is recommended that reading be made forty-eight hours afterward, when early reactions will not have disappeared and some late reactions will have developed The patient should be advised to inform his physician if later reactions occur "

The interpretation of the reaction is described in the articles of Vollmer and Goldberger (9) and in the circular of the Lederle Laboratories as follows

"A positive reaction appears as sharply circumscribed, infiltrated and reddened squares with lichenoid-follicular elevations The central control square appears pale Individuals with sensitive skin occasionally show a nonspecific irritation due to the adhesive, which does not interfere with the reading of the reaction, as in the case of a negative reaction the areas covered by the tuberculin squares appear paler than the surrounding skin and in the case of positive reactions the square areas appear of a more intense red Quantitative degrees can be differentiated if desired as follows

One plus—A few lichenoid efflorescences

Two plus—Lichenoid-follicular eruptions assembled in clear-cut square

Three plus—Confluent eruption with marked induration and elevation in square form

Four plus—Spread of the cutaneous reaction beyond the square area or blister formation ”

#### SURVEY OF THE LITERATURE OF THE PATCH TEST OF VOLLMER

Up to the present date there exist 19 publications dealing with a total of 8,594 subjects in whom the tuberculin patch test of Vollmer has been compared with other accepted standardized tuberculin tests. For various reasons all of these findings cannot be pooled together and evaluated collectively. In some reports the standardized control has been the Pirquet test, in others it has been the Mantoux test. When the Mantoux test was employed the dosage has covered a wide range, 0.1, 0.1, 1.0 and even 10.0 mg. Old Tuberculin have been used. Some investigators have preferred Purified Protein Derivative to Old Tuberculin. Some have considered a reaction to be positive only when induration reached a diameter of 10 mm, others have been satisfied with an infiltrative reaction 5 mm in diameter. Moreover, some investigators have dealt with children and others with adults. Finally, and perhaps of primary importance for our purpose of appraisal, some studies were carried out in institutions in which presumably all of the subjects were infected with tuberculosis while others were made on populations with a relatively low incidence of infection.

In reviewing these heterogeneous data it is clear that answers to two questions must be sought. Both questions concern the reliability of the patch test. The first deals with groups of infected subjects and asks what percentage of the cases will be missed by failure to show a positive test. The second deals with groups of uninfected subjects and asks what percentage will be improperly diagnosed as infected by the occurrence of false positive reactions. Unfortunately, a completely satisfactory answer to these questions cannot be attained since there is no way of distinguishing in the available data between infected and uninfected subjects except in terms of the control tuberculin test. The situation is further complicated by the circumstance that some authors have not distinguished between the negative reaction in an infected subject and the possibly false positive reaction, in these articles the percentage discrepancy or failure of conformity between the two tests is reported without distinction between the two types of unreliable tests. Indeed, in some papers discrepancies in individual patients are not recorded at all, the author merely giving the total number of positive and negative reactions to the two tests.

For the reasons cited above it has seemed wise to utilize for general appraisal data from only 9 of the 19 reports in the literature. These data deal with a total of 4,162 tests. In all of them the control test was performed by the Mantoux technique in dosages which were always increased to 10 mg or more of Old Tuberculin or to a biologically equivalent amount of Purified Protein Derivative.

The summary of these data, given in table 1, was prepared on the assumption that the control tests were adequate for separating infected and noninfected subjects. Because the assumption cannot be accepted without reservation, interpretation must allow for some error in the accuracy of the separation. The uniform arrangement of the data in the table was made to fit the purpose of critical review, the summaries are not in the form in which they were presented by the authors. For each article the total number of tests is given together with the distribution of the results among the four possible categories, namely, both tests negative, both tests positive, control test positive and patch test negative, control test negative and patch test positive. Computations presented in the last two columns give the information concerning the percentage of discrepancy between the two tests. The method of computing these percentages, outlined in principle above, can be illustrated by the 169 tests of Vollmer in 1938. Here the control test indicated that 166 of the subjects were infected and, of these, 165 were identified by the patch test and one was not. Failure of the patch test to identify infection is therefore listed as one in 166, or approximately 0.5 per cent. Conversely the control test indicated that 3 of the 169 subjects were not infected and, of these, one gave a positive reaction to the patch test. The false positive reactions are therefore listed as one in 3, or 33 per cent. From the illustration it will be clear that the percentages have little meaning in reports where only a few cases are involved, also that the designation "false positive" should not be taken too literally since such a result will be tabulated when the control test has failed to identify an infection which led to a legitimately positive patch test. The totals for all authors show 1,856 control-positive subjects with failure of identification by the patch test in 270, or 15 per cent, and 2,306 control-negative subjects with false positive reactions in 78, or 3 per cent. Although there is no good reason for eliminating the results of individual investigators it is of interest to note that 67 of the total of 78 false positive reactions were recorded by Pearse. If these data are removed from the totals, the percentage of false positives falls to 0.6 per cent. Conversely 225 of the

270 instances in which the patch test failed to identify infection were recorded by Peck. If his data are removed from the totals the failures

TABLE 1

*Summary of the literature of the tuberculin patch test of Vollmer*

AUTHOR	TOTAL NUMBER OF CASES	CONTROL TUBER- CULIN	BOTH TESTS NEGATIVE	BOTH TESTS POSITIVE	CONTROL POSITIVE, PATCH NEGATIVE	CONTROL NEGATIVE, PATCH POSITIVE	PER CENT FALSE NEGA- TIVE PATCH TEST	PER CENT FALSE POSI- TIVE PATCH TEST
Vollmer 1938	169	PPD	2	165	1	1	1/166 0.5%	1/3 33%
Vollmer 1938	118	OT	106	10	—	2	—	2/108 2%
Hart	536	OT	436	97	3	—	3/100 3%	—
Leonidoff	189	PPD	2	185	2	—	2/187 1%	—
Vollmer 1939	251	OT PPD	4	245	1	1	1/246 0.4%	1/5 20%
Peck	880	PPD	561	94	225	—	225/319 71%	—
Hughes	100	PPD	—	89	11	—	11/100 11%	—
Pearse	712	PPD	492	132	21	67	21/153 14%	67/559 12%
Vollmer 1940	667	OT	616	41	4	6	4/45 9%	6/622 1%
Vollmer 1940	540	PPD OT	9	528	2	1	2/530 0.4%	1/10 10%
Totals	4,162	OT PPD	2,228	1,586	270	78	270/1,856 15%	78/2,306 3%

Note. The control test consisted of 0.01 to 10.0 mg Old Tuberculin intracutaneously or its equivalent in PPD.

become 3 per cent instead of 15 per cent. Comment on these discrepancies of observation will be reserved until the results of our own experience have been presented.

## OUR EXPERIENCE WITH THE PATCH TEST

In 1938 and again in 1940, we had an opportunity in the New York Institute for the Education of the Blind to compare in a group of school children the tuberculin patch test with Mantoux tests done with 0.01 and 1.0 mg Old Tuberculin, 177 subjects were tested in 1938 and 202 in 1940. There were 163 pupils who occurred in both series.

In reading the Mantoux test, we adhered to the standards of the National Tuberculosis Association, described by Aronson (19) as follows:

"A reaction showing some redness and definite oedema more than 5 mm., and not exceeding 10 mm. in diameter, is recorded as a one-plus reaction. A two-plus reaction is an area of redness and oedema measuring from 10 to 20 mm. in diameter. A three-plus reaction is characterized by marked redness and oedema exceeding 20 mm. in diameter. A four-plus reaction consists of marked redness, oedema and an area of necrosis. A reaction with slight redness and a trace of oedema, measuring 5 mm. or less in diameter, is marked doubtful. If there is no oedema at the site of injection, even if a slight redness is present, the test is recorded as negative. In interpreting the tuberculin reaction it must be remembered that the redness has less significance than the oedema."

In reading the patch tuberculin test we followed the standards of the originator of the test, Dr. Hermann Vollmer (9), who was kind enough to read most of the tests with us. To avoid bias the readings were made in such a way that the result of the Mantoux test should not be known while the patch test was being examined.

The Mantoux tests were done with Old Tuberculin, furnished by the Department of Health of the City of New York.

The material for the patch tuberculin test was placed at our disposal by the Lederle Laboratories, Inc. In 1938, the patches were manufactured with regular Old Tuberculin of the Department of Health of the City of New York. In 1940, the patches were made with Old Tuberculin produced on synthetic media according to the Seibert method (20). Vollmer (3) states that the latter tuberculin is four times more potent than the type grown on beef broth, available in 1938.

The results from this series of observations are presented in table 2. The combined data for the two years show 31 negative patch tests in 114 Mantoux-positive children, that is, failure to identify infection in 27 per cent. Among 265 Mantoux-negative subjects there were 28 positive

patch tests, that is, an incidence of false positive reactions of 11 per cent. Since in both classes of unreliable tests the percentage of discrepancy is considerably higher than was observed by other investigators (table 1), these findings require additional comment.

With respect to failure of the patch test to identify infection demonstrable by the Mantoux test the results for the two years, 31 per cent in 1938 and 25 per cent in 1940, are consistent. Reference to table 1 shows that these figures are well above the 15 per cent, representing the combined experience of other authors, but below the individual experience of Peck who found such failure in 71 per cent. Wide divergencies of this type inevitably suggest that differences in technique in performing the test have influenced the results. We have done our best to avoid such

TABLE 2

*Summary of the comparative value of Mantoux and patch tests done in the New York Institute for the Education of the Blind*

YEAR	TOTAL NUMBER	BOTH TESTS NEGATIVE	BOTH TESTS POSITIVE	CONTROL POSITIVE, PATCH NEGATIVE	CONTROL NEGATIVE, PATCH POSITIVE	PER CENT FALSE NEGATIVE PATCH TEST	PER CENT FALSE POSITIVE PATCH TEST
1938	177	125	31	14	7	14/45 31%	7/132 5%
1940	202	112	52	17	21	17/69 25%	21/133 16%
1938 and 1940	379	237	83	31	28	31/114 27%	28/265 11%

Note. The control test consisted of 0.01 to 1.0 mg. Old Tuberculin intracutaneously.

errors but some have undoubtedly occurred. While the patches were on, the children refrained from physical activity in order to prevent excess perspiration. If, by accident, a patch came off prematurely, the test was repeated. In Peck's cases the existence of technical factors as causes of variability in response is indicated by his results when the patch test was repeated. Among 52 Mantoux-positive subjects who exhibited negative patch tests, repetition of the test yielded a positive result in 16 instances. Similarly in our series, among 30 cases where the patch test failed to identify infection, repetition of the test gave a positive result in 12 instances. We shall show presently that most of these difficulties arise in subjects in whom allergy to tuberculosis is low and where it is necessary to appraise the significance of borderline reactions. In reading

such tests it is almost impossible to avoid a personal bias, if the result of one test is known when the other is inspected. Some of the extremely low figures in the literature for failure of the patch test to identify infection may find their explanation in this circumstance.

The considerations outlined above lead to the conclusion that the patch test is capable of highly reliable results when performed under ideal conditions. Some of these conditions can be controlled by care in applying the test but unfortunately some, which depend on the co-operation of the subject, the season of the year and other factors influencing perspiration, cannot be controlled and will remain as causes of discrepant results.

The high incidence of false positive reactions shown in table 2 also demands comment. Here the figures for the two years, 5 per cent in 1938 and 16 per cent in 1940, are not consistent and indicate a statistically reliable increase in the incidence of such reactions. The reason for the increase is not entirely apparent. Subjective change in the attitude of the observer over the period of two years may have exercised some influence on the result. However, it should be noted that during the interim the tuberculin used in the patch test outfits was changed from material prepared on beef broth to material prepared on synthetic medium. Steward (14) also found that incidence of positive patch tests with negative Mantoux tests rose from 4 per cent to 8 per cent in a series of 48 subjects when tuberculin prepared on synthetic medium, instead of beef broth, was used.

Before commenting on the significance of these false positive reactions, it will be helpful to consider both types of unreliable patch tests from the standpoint of the degree of allergy exhibited by the subjects on whom the tests were performed. In our series there were 59 instances of contradiction between the two types of tuberculin tests. In 36 of these the induration of the Mantoux test was only 10 mm or less in diameter and in 54 the patch test was recorded as only one-plus. Thus the majority of discordant results were obtained on subjects who exhibit slight or dubious reaction to tuberculin, the significance of false positive reactions must be viewed in this light. The criteria of the National Tuberculosis Association, used by us in reading the Mantoux test, represent the result of long and large experience. In drawing them up it was clearly recognized that no test for allergy can distinguish infallibly between infected and noninfected subjects, that it is wiser to overlook and set aside for further study, subjects in whom the presence of infection is dubious than



to brand as infected subjects in whom no infection is present. Undoubtedly, in its present form and with the present criteria for reading, the patch test will disclose the presence of tuberculous infection in cases where the Mantoux test has failed but it follows for the same reason that it will label as tuberculous a certain number of subjects in whom no infection is present.

In viewing both types of unreliable reactions collectively, it is clear that any attempt to decrease the incidence of false positive reactions by assuming a more conservative attitude in interpreting mild reactions must also increase the incidence of failure to identify the presence of infection. Undoubtedly a more rational method of interpretation can be reached. But it is clear that the period has not yet arrived when the time-proven Mantoux test can be replaced by an equally reliable contact test.

#### SUMMARY

The literature dealing with the tuberculin patch test has been reviewed in order to tabulate all instances in which the reaction was compared with an adequately performed Mantoux test. There is considerable variability among the findings of different authors. Therefore the pooled results might have to be changed at a later date when more and more homogeneous material will be at our disposal. The present combined data show that 15 per cent of Mantoux-positive subjects have exhibited a negative patch test, that 3 per cent of Mantoux-negative subjects have given a positive patch test.

Personal experience with comparative patch test and Mantoux test on 379 school children showed that 27 per cent of Mantoux-positive subjects exhibited a negative patch test while 11 per cent of Mantoux-negative subjects gave a positive patch test.

The discrepancies in the results of different investigators are discussed in order to assist in assessing the reliability of the patch test.

#### CONCLUSION

The tuberculin patch test, because of simplicity of performance, has a limited field of usefulness. Evidence so far available does not indicate that it can be used to replace in reliability the well established Mantoux test.

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## CLINICAL AND LABORATORY NOTES

### TUBERCULOSIS IN IDENTICAL TWINS<sup>1,2</sup>

G D KETTELKAMP AND WILLIAM W STANBRO

Chester and Chesley, white male, identical twins, aged seventeen, were admitted to Robert Koch Hospital on August 5, 1939, with a diagnosis of far advanced pulmonary tuberculosis. There was no hospital record of their birth, since they were delivered at home by a physician who is now dead. However, the mother states that she was told by the physician who attended her that "both babies were in the same sac and that there was only one after-birth." Under like environment the course of development of the twins was similar. Chesley was a little larger than Chester but otherwise they looked very much alike. To the childhood diseases, which they had at the same time, their behavior was similar. The family history was negative for tuberculosis and there was no history of outside exposure to tuberculosis in either case.

Because of the remarkable similarity in the behavior of the twins to tuberculosis it was felt that the cases were of sufficient interest to report. In reviewing the literature it was found that this similarity in behavior of identical twins to pulmonary tuberculosis had been emphasized in several reports. Uehlinger and Kunsch (1) reported tuberculosis in 46 pairs of twins, 12 of whom were identical and 34 of whom were fraternal. Their results were as follows:

In the 12 pairs of identical twins the behavior to tuberculosis was similar in 7 and dissimilar in 5, in the 34 pairs of fraternal twins the behavior to tuberculosis was similar in 2 and dissimilar in 32. These figures are even more striking when environment is considered. In the 12 pairs of identical twins environment was similar in 7 and dissimilar in 5, in the 34 pairs of fraternal twins, the environment was similar in 25 and dissimilar in 9.

Uehlinger and Kunsch also gave, in their article, the results of Diehl and Verschuer which were as follows:

In 80 pairs of identical twins the behavior to tuberculosis was similar in 52 and dissimilar in 28, in 125 pairs of fraternal twins the behavior to tuberculosis was similar in 31 and dissimilar in 94.

Verschuer (2) reported 36 pairs of identical twins and 43 pairs of fraternal twins with tuberculosis in which the behavior was similar in 25 and dissimilar

<sup>1</sup> From the Robert Koch Hospital, Hospital Division, Department of Public Welfare, St. Louis, Missouri.

<sup>2</sup> Read before the St. Louis Trudeau Club, May 2, 1940.

in 11 of the identical twins, whereas in the fraternal twins the behavior was similar in 9 and dissimilar in 34

Diehl (3) reported tuberculosis in 104 pairs of twins. In the 36 pairs of identical twins the behavior was similar in 25, or 69 per cent, and dissimilar in 11, or 31 per cent, whereas in the 68 pairs of fraternal twins the behavior was similar in 17, or 25 per cent, and dissimilar in 51, or 75 per cent

Elizabeth Klein (4) reported tuberculosis in identical twins in which both died at ten and eleven months, respectively, and in which one of the pair developed a haematogenous spread with a resultant generalized miliary tuberculosis

### CASE REPORTS

#### CHESTER

#### CHESLEY

#### *Clinical Histories*

Onset November, 1938 with a pain in the left side of the chest, cough and expectoration. Pulmonary tuberculosis was diagnosed in March, 1939. He was hospitalized in March, 1939. A left therapeutic pneumothorax was induced in June, 1939.

Onset in January, 1939 with pain in the left side of the chest, cough and expectoration. Pulmonary tuberculosis was diagnosed in April, 1939. A left therapeutic pneumothorax was begun in June, 1939.

#### *Positive Findings on Admission to Robert Koch Hospital*

T 101 7, P 110, R 26  
Height 61 inches, Weight 89½ lbs  
General appearance poorly developed, emaciated and very weak

Eyes left eye artificial as a result of an accident

Ears negative

Chest Left side percussion note hyperresonant, tactile fremitus diminished, vocal resonance diminished, breath sounds suppressed, no râles

Right side negative

T 100 2, P 104, R 24  
Height 61¼ inches, Weight 101¼ lbs  
General appearance poorly developed, undernourished and weak, but somewhat stronger than Chester

Eyes negative

Ears chronic suppurative otitis media, left

Chest Left side percussion note hyperresonant, tactile fremitus diminished, vocal resonance diminished, breath sounds suppressed, few râles in apex

Right side negative

*Laboratory Findings*

Urine negative  
 Sputum positive for acid-fast bacilli  
 Kahn negative  
 W B C 9,350  
 Differential—39% segmented, 3%  
 eosinophiles, 9% monocytes, 37%  
 stabs, 12% lymphocytes  
 R B C 3,250,000  
 Hb 55%

Urine negative  
 Sputum positive for acid-fast bacilli  
 Kahn negative  
 W B C 10,700  
 Differential—43% segmented, 1%  
 eosinophiles, 1% basophils, 4%  
 monocytes, 27% stabs, 24% lym-  
 phocytes  
 R B C 3,900,000  
 Hb 72%

*Röntgenological Examination*

Left pneumothorax in which there was a fairly good collapse. There was a small amount of fluid in the left base. The markings in the right lung were rather heavy.

Pneumothorax on the left in which there was a moderate collapse. There were several long adhesions to the apex. There was a moderately heavy infiltration throughout the middle third of the right lung.

*Hospital Course*

The left pneumothorax was continued with weekly refills of 400 to 600 cc of air, beginning and ending with negative pressures. The mediastinum was very labile. He did poorly, going downhill progressively, with daily elevations in temperature and a steady decline in weight. He developed hoarseness and pain in his throat on swallowing. He suffered with bouts of diarrhoea and abdominal cramps. On December 9, 1939, about five days after his last pneumothorax refill, he developed a left spontaneous pneumothorax. Air was removed on five occasions in the next three days for relief of dyspnoea.

The left pneumothorax was continued with weekly refills of 400 to 600 cc of air, beginning and ending with negative pressures. The mediastinum was very labile. He did poorly, going progressively downhill with daily elevations in temperature and a steady decline in weight. He became hoarse. He developed an obstinate diarrhoea, frequently accompanied by severe abdominal cramps. On October 4, 1939, several days after his last pneumothorax refill, he developed a left spontaneous pneumothorax. Air was removed from the left chest on two occasions for relief of dyspnoea. He developed fluid on

and thereafter air was removed once a week. On March 5, 1940, the air removed from his left chest had a very foul odor. He died on the evening of March 5, 1940, the disease having progressed with no remissions from date of admission.

the left which, with discontinuation of the left pneumothorax and re-expansion of the lung, was absorbed. He died on February 11, 1940, there having been no remissions in the progress of his disease.

### *Autopsy Findings*

- |   |  |
|---|--|
| <p>1 The left pleural cavity was filled with thin foul-smelling pus</p>   | <p>1 The right pleural cavity contained 300 cc of a cloudy straw-colored fluid</p>   |
| <p>2 The larynx showed marked oedema of the epiglottis and arytenoids with extensive ulceration extending downward to involve both the false and true cords. Microscopical examination revealed numerous tubercles, only a few of which contained giant cells.</p>  | <p>2 The larynx showed a small circumscribed ulcer about 0.5 cm in diameter on the right true cord.</p>  |
| <p>3 The trachea showed extensive ulceration with numerous tubercles on microscopical examination.</p>  | <p>3 In the left main bronchus, about 1 cm distal to the carina, there was a roughening of the mucosa which on microscopical examination showed several non-giant cell-containing tubercles.</p>   |
| <p>4 The left lung was collapsed to one-half its usual size and a broncho-pleural fistula was present. Numerous large caseous tubercles, none of which were encased in a fibrous capsule, and only a few of which contained giant cells, were present. There were several small cavities. Numerous caseous tubercles and several thin-walled cavities were present in the right lung.</p> | <p>4 On the surface of the right lung were numerous caseous tubercles. There was no portion of the right lung which was not involved either in the form of tubercles or cavities. The left lung showed several cavities in the upper lobe and caseous tubercles scattered throughout the remainder of the lung. No giant cells were found in these tubercles and no fibrous tissue capsules surrounded them.</p> |
| <p>5 Microscopical examination of the liver and spleen revealed several tubercles.</p>  | <p>5 The liver and spleen showed microscopical tubercles.</p>  |
| <p>6 Beginning in the lower part of the</p>   | <p>6 Beginning in the first part of the</p>  |

jejunum and extending distally to involve the remaining small bowel and the entire large bowel, were numerous ulcerations which microscopically revealed tubercles of the giant cell and non-giant cell-containing varieties

7 Microscopical examination of appendix showed several tubercles

8 No tuberculosis of kidneys found

jejunum and extending throughout the remainder of the small bowel and all of the large bowel were numerous ulcerations

7 Microscopical examination of the appendix revealed a small non-giant cell-containing tubercle

8 In the cortex of the right kidney there was a small yellow nodule which on microscopical section was found to consist of several tiny conglomerate tubercles

#### DISCUSSION

It is felt that the similarity of behavior in this instance of tuberculosis in identical twins is the result of identical inheritance. This conclusion is borne out by the results given in the discussion of the literature. Although in this particular instance the environment was similar, Uehlinger and Kunsch point out that in spite of the fact that in their series the fraternal twins had similar environment in 73 per cent of the cases, only 5 per cent were similar in their behavior to tuberculosis, while identical twins had similar environment in only 58 per cent of the cases and still 58 per cent were similar in their behavior to tuberculosis. Another point of interest in these cases is the likeness of the tissue response to the tuberculous infection. In both twins there was a paucity of giant cells and no evidence of fibrous tissue capsules about tubercles.

#### SUMMARY

Chester and Chesley, seventeen years old, identical twins, entered Koch Hospital on August 5, 1939 with a history of common initial symptoms of pain in the left chest, cough and expectoration. A therapeutic left pneumothorax had been started on them both in June, 1939. The clinical course was similar, both going progressively down-hill, both developing symptoms of laryngeal and intestinal tuberculosis and both developing left spontaneous pneumothorax several days after their last refill. Postmortem examination revealed each to have tuberculosis of the lung, larynx, intestines, liver and spleen. In both there was a paucity of giant cells and no evidence of fibrous capsules about tubercles.

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## EYE COLOR AND TUBERCULOSIS<sup>1, 2</sup>

EMIL BOGEN

The phthisic diathesis of Hippocrates, as well as the quite contrary scrofulous diathesis of Hufeland, agree in characterizing the form of the body peculiarly subject to this complaint as possessing blue eyes (1) Although this concept has been less emphasized in recent years, its persistence in textbooks and other literature seemed to justify an attempt at its quantitative verification

The color of the eyes has been recorded for all patients admitted to the Olive View Sanatorium during the past two decades For the purpose of this study, all of the darker colored eyes, described as black, brown, dark brown, light brown or gray brown, have been considered together as contrasted with the lighter group of blue, light or dark blue, blue gray, gray, hazel or green eyes

We do not have any information as to the actual frequency of distribution of the different eye colors in the entire community, and so the fact that more dark-eyed individuals were admitted together than light-eyed individuals, may not be interpreted to mean that dark-eyed persons are more apt to develop the disease

The stage of disease, at the time of admission, in patients with the different colored eyes was, in general, quite similar, about two-thirds of both groups being far-advanced at the time of admission Slightly less dark-eyed individuals were admitted in the minimal stage, however This may reflect the fact that dark eyes are more common in the Mexicans and Negroes who are less frequently diagnosed early, perhaps chiefly because of cultural and environmental factors (2)

The course of the disease, after admission to the Sanatorium, however, is less affected by these previous environmental differences Here, it is found that there has been practically no difference The case fatality rate among patients in the three different stages of the disease, cared for at the Olive View Sanatorium, has been practically the same in patients with light and dark pigmented eyes (3) Differences in individual susceptibility to tuberculous infection may exist in different groups, but it does not appear likely that any

<sup>1</sup> From Olive View Sanatorium, Olive View, California

<sup>2</sup> With the aid of Work Projects Administration, Project No 665-07-3-223, Los Angeles County, California

such differences are associated with differences in the pigmentation on the iris of the eye

*Eye Color and Tuberculosis*

	DARK EYES				LIGHT EYES			
	Patients	Died	Years followed	Per cent	Patients	Died	Years followed	Per cent
Minimal	403	24	1,980	1 2	368	30	2,204	1 3
Moderate	674	92	2,324	4 0	421	85	1,676	5 0
Far advanced	3,203	1,776	7,994	22 2	2,438	1,382	6,648	20 8
Childhood and nonpulmonary	605	41	2,588	1 6	333	27	1,512	1 7
Total	4,885	1,933	14,886	13 0	3,560	1,524	12,040	12 7

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## FIBRIN-BODIES IN PNEUMOTHORAX<sup>1</sup>

W H OATWAY, JR

Fibrin-bodies are considered to be concretions of fibrin which occur in the presence of fluid. They may form free or attached to adhesions. They may remain for long periods, may degenerate, may organize (if attached to a blood supply) or may disappear. They may also have peculiar complications.

Fibrin-bodies have not uncommonly been described in cases of intrapleural pneumothorax. Recent articles on extrapleural pneumothorax have contained occasional references to the possibility of fibrin-body formation, and one author has noted this occurrence in his series.

Two instances of fibrin-body formation in extrapleural pneumothorax are reported here. Each developed in the presence of fluid. One occurred shortly after operation, the other six months later. Both were apparently unattached. One was solid, but slowly liquefied after the induction of oleothorax, and the other became inflated during the aspiration and replacement of fluid with air.

*Case 1* A white male, aged thirty-nine. The original lesion was chronic, bilateral, apical with moth-eaten cavitation. A healed Pott's disease of twenty years' duration had left an S-shaped kyphoscoliosis. Intrapleural pneumothorax was impossible on either side. An extrapleural pneumothorax was induced in the upper third on the right side, and considerable serosanguineous fluid formed after operation. This was aspirated with some difficulty due to the kyphosis. At the end of a week it was obvious that an amorphous body was present in the residual fluid, and this gradually assumed an oval shape with no mural connection. (See films of case 1, (a) and (b).)

Five months after the operation the pneumothorax was unchanged, the fibrin-body was slightly smaller, and a small amount of thick, sterile, tan-colored fluid was present. The pneumothorax was converted to oleothorax without incident. A few cc of fluid have been aspirated at intervals since (although the oil pressures have not risen), and the fibrin-body disappeared. It is probable that the free fibrin-body slowly liquefied.

*Case 2* A white female, aged twenty-eight. The original lesion was unilateral and caseo-pneumonic. Intrapleural pneumothorax was inefficient because of

<sup>1</sup> From the Thoracic Service, State of Wisconsin General Hospital, and Medical School, University of Wisconsin, Madison, Wisconsin.

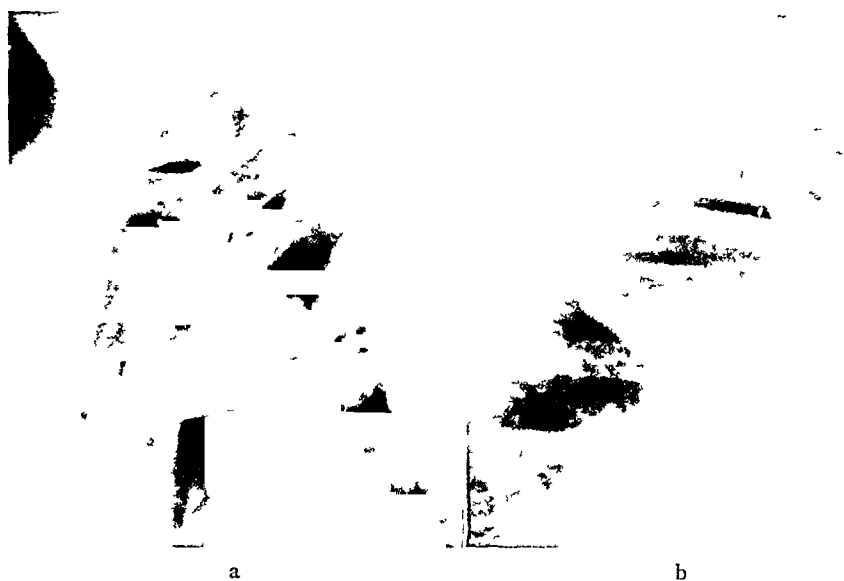


FIG 1 Case 1 (a) Left Patient tilted to his right (b) Right Patient tilted to his left, fibrin-body moves freely

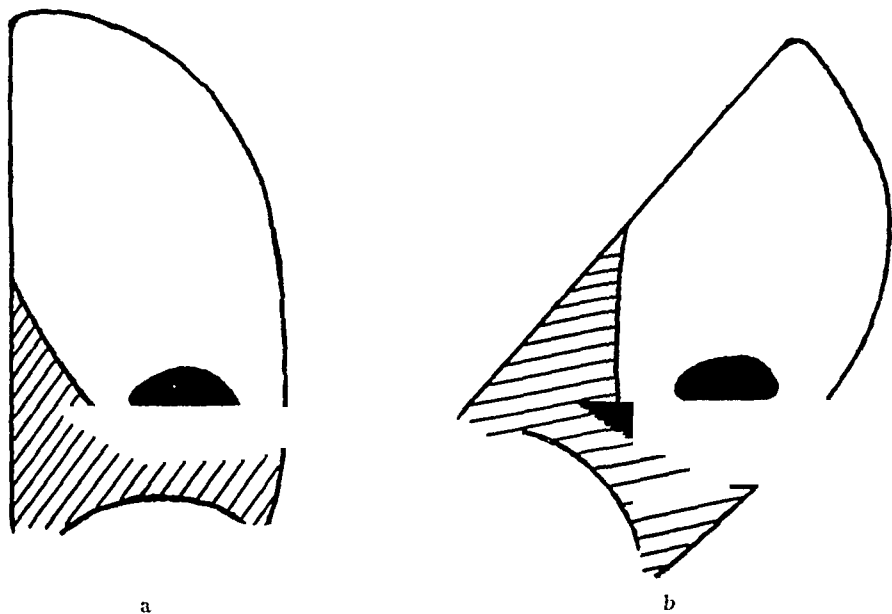


FIG 2 Case 2 Floating, inflated fibrin body (a) Left Patient erect (b) Right Patient tilted to her left

adhesions, and later the lung could not be reexpanded. A phrenic crush was of no help. The bronchi were clear.

A large extrapleural pneumothorax was then done, with a good collapse of the lung. The course was uneventful for six months, when a clear fluid began to form. After weekly aspirations, the formation decreased and oleothorax was attempted. Because of continued effusion the oil was removed. A few weeks later a fibrin-body was noted, about 4 x 7 cm in size, unattached and floating in the fluid. This came down against the tip of the needle at the end of each aspiration. After several weeks and at the conclusion of an aspiration with replacement of the fluid by air, fluoroscopy showed a peculiar phenomenon which was confirmed by X-ray films. The fibrin-body had become inflated during the aspiration procedure. (See X-ray drawings of case 2.) A month later, and over a period of two weeks, the fibrin-body disappeared, with no change in the clear quality of the fluid.

## TRAY FOR STAINING TUBERCLE BACILLI<sup>1</sup>

WILLIAM STEENKEN, JR

One of the most frequent criticisms of the staining for tubercle bacilli of many slides in the same jar at the same time, is that negative smears may become contaminated with acid-fast organisms from highly positive smears.

To answer this criticism a tray has been designed to stain at one time 6 slides, smeared with sputum or other tuberculous material. It may be used for rapid, or overnight staining of such preparations.

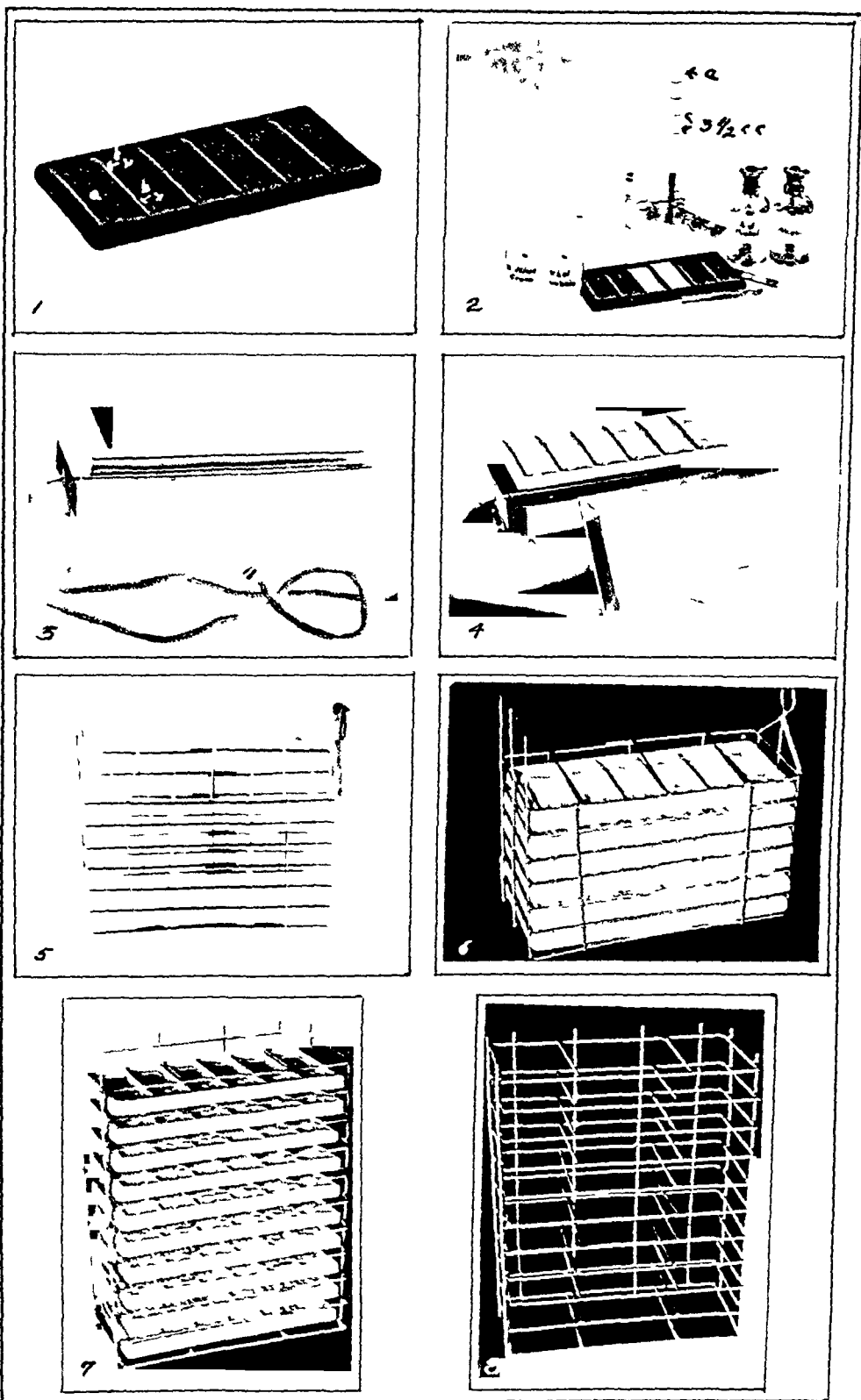
*Rapid method* If the tray is used for rapid staining, carbol fuchsin is added, with the aid of a pipette or burette (figure 2-a), to each small compartment (figure 1-a) until the small elevations (figure 1-b) are covered with the dye (The height of the elevations is fixed so that the amount of stain required to cover them—3.5 cc—will be approximately the same as that used for flooding a slide.) The smears are then fixed by heating and placed, *smear side down*, in each compartment of the staining tray. The tray is now placed in a small electric oven (figures 3 and 4) and heated at 50°C for approximately fifteen minutes and is then taken out of the oven and allowed to cool. Each slide is removed from the tray and decolorized separately, first with acid alcohol, then alcohol, and finally counterstained with brilliant green, or methylene-blue, as one may prefer.

*Overnight method* The overnight method is especially helpful when large numbers of specimens are to be examined. It allows one day for the preparation and smearing of the specimens, and the next day for decolorizing, counterstaining and microscopical examination.

The slides are prepared in the same manner as for rapid staining and placed in the trays containing the dye. The trays are then placed in wire racks (figures 5, 6, 7 and 8), and set in a humidifier in the incubator at 37.5°C overnight. The following morning the wire rack containing the trays is removed, and the trays cooled at room or icebox temperature. The slides are then removed from the compartments and washed, decolorized and counterstained separately as previously mentioned.

The stain employed in these trays is prepared according to Cooper (1) with the exception that in this laboratory 0.5 cc instead of 3.0 cc of 10 per cent sodium chloride per 100 cc of Ziehl-Neelsen carbol fuchsin is used.

<sup>1</sup> From the Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, New York.



FIGS 1-8

## DISCUSSION

The criticism that acid-fast organisms may be transferred from slide to slide is a just one, but experimental data are lacking to prove that acid-fast organisms from highly positive slides may contaminate negative smears when stained in the same jar and in the same solution at one time

Often smears that are reported as negative by the regular routine examination—twenty minutes—are found to be positive after prolonged microscopical inspection, and conversely, smears that contain a few acid-fast organisms, as revealed by the routine examination, may be considered as negative after repeated inspection by another examiner. It is, therefore, difficult to prove whether or not contamination with acid-fast organisms has taken place

However, to guard against the possibility of contamination we have adopted this multiple staining technique, whereby each slide is stained individually in the same unit at the same time

The tray and small heating oven described for this purpose is well suited for use in small laboratories that do not have gas

The trays are made of glazed porcelain so that they can and should be burned out with cleaning solution (sulphuric acid and potassium dichromate) between each use in order to prevent any possible carrying over of acid-fast organisms from one slide to another

The complete staining equipment may be obtained from The Will Corporation, Rochester, New York

## REFERENCE

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- FIG 1 Porcelain staining tray  
FIG 2 Burette used for adding stain to small compartments of tray  
FIG 3 Heating oven closed  
FIG 4 Heating oven containing staining tray  
FIG 5 Small wire rack  
FIG 6 Small wire rack containing staining trays  
FIG 7 Large wire rack containing staining trays  
FIG 8 Large wire rack



## COMMUNITY SURVEY FOR TUBERCULOSIS<sup>1</sup>

ROBERTS DAVIES AND CHARLES S. ROBB

For many years tuberculosis workers have hoped for eventual eradication of the disease. Yet, despite declining death rates, eradication appears unlikely with present methods of control. Pessimism regarding the ultimate effectiveness of examination of contacts and segregation and treatment of active cases seems to be well founded. The fact that few, if any, communities have actually been able to examine adequately and repeatedly all contacts of open cases and to segregate all active cases throughout the period of activity indicates a practical if not a theoretical defect in the method.

Patients with active disease often give no history of exposure to tuberculosis and frequently examination of all their intimate contacts fails to reveal a source of infection (1). In some cases, more or less casual contact may be of more significance than is ordinarily assumed. In others, especially in older age groups, the disease may represent reactivation of a latent lesion many years after the original contact was broken. At any rate such cases show that the most thorough contact-examination program cannot hope to find all the active cases of tuberculosis in a community, much less find them in an early stage of their disease.

Partly because of the recognized deficiencies in our present programs, there has been a growing interest in mass surveys designed to find all the tuberculosis in a given group. Surveys of schools, factories and various public institutions have been reported with increasing frequency.

In 1937, Nopeming Sanatorium and the St. Louis County Health Department made a tuberculin and X-ray survey of the entire population of a rural township (1). Six new cases of tuberculosis were found in a community of 367 persons. Since that time several reports of similar complete community surveys have appeared (3, 4, 9) and the importance of mass surveys of special population groups has been emphasized (5, 6, 7, 9, 10). An especially valuable contribution is the report of H. R. Edwards on the surveys made by the New York City Department of Health (2).

In the summer of 1939, Nopeming Sanatorium made another survey of three more townships in St. Louis County. Our method was the same as that used in our previous survey. We visited each house in the community, explained the purpose of the survey, took a brief history of the family, and gave tuber-

<sup>1</sup> From Nopeming Sanatorium, Nopeming, Minnesota.

culin tests to everybody The first skin test was given with the usual first-strength dose of 0.000,02 mg of PPD Reactions were read in forty-eight hours and all negative reactors were given a second test of 0.002,5 mg of PPD, or one-half the usual second-strength dose Positive reactors were brought to the Sanatorium for X-raying Single 14" by 17" chest plates were taken at 72" with 0.1 second exposure, using 100 milliamperes and from 66 to 90 kilovolts All films were read either by Dr G A Hedberg of the Sanatorium staff or by the senior author

The total population of the communities studied is 1,215 Approximately 77 per cent of the population is Finnish, 12 per cent, Scandinavian, and 11 per cent belong to other nationalities About 35 per cent of the population is foreign-born Most of the people make a living on their farms The soil is relatively unproductive and the people are poor

Of the 1,215 people in the three communities, 116, or 9.5 per cent, were not adequately examined Some of these had negative first-strength tuberculin tests but no repeat skin test or X-ray examination, some had positive tuberculin tests but no X-ray film, and a few were not examined at all Sixty-two, or 5 per cent, refused examination

The distribution of positive reactors by age, sex and nationality revealed nothing of particular interest Fifty-five per cent of the males and 46 per cent of the females had positive tuberculin reactions Forty-one per cent of the reactors were positive only to the second test Fifty-three per cent of the Finnish people and 47 per cent each of the Scandinavian and the group of "other nationalities" had positive skin tests These percentages are corrected for age distribution There is no mathematical assurance that the slight differences observed between nationalities could not be due to chance

Of the 572 persons X-rayed, 349 were negative, 46 had evidence of pleurisy only, 75 showed evidence of primary infection, and 52 showed secondary or adult-type tuberculosis Only one case had a lesion that appeared active This man was immediately hospitalized and treated All cases showing secondary lesions were filed for repeat films

The great difference in the number of new cases of active tuberculosis found in our two surveys (6 from a population of 367 compared to 1 from a population of 1,215) probably reflects a real difference in the tuberculosis status of the communities involved, since there is a similar difference in percentage of positive skin tests and of apparently inactive adult-type lesions The comparable percentages after correction for differences in age distribution are first survey—positive reactors 59 per cent, inactive lesions 15 per cent, second survey—positive reactors 52 per cent, inactive lesions 7 per cent Only 3 times in 100 could such a difference in positive skin tests be due to chance and only once in 500 times would such a difference in the incidence of inactive lesions occur by chance

These differences in the two communities possibly reflect the differences in percentage of foreign-born persons. In the first survey, 65 per cent were foreign-born and in the second survey only 35 per cent. In comparable age groups 86 per cent of foreign-born persons had positive skin tests as compared with 64 per cent of those of native birth. Age, nationality, sex and economic status do not seem to be significant factors in explaining the differences between the two communities, since correction was made for variation in age distribution, the three nationality groups showed no significant differences in percentage of positive reactors or X-ray lesions, and sex distribution and economic status did not vary significantly between the two survey groups.

Complete community surveys such as these are expensive and for that reason inefficient, except where the incidence of clinically important tuberculosis is unusually high. However, the recent development of fluorographic methods, by greatly reducing the cost of X-ray examination and eliminating the need for tuberculin screening, may make much more extensive application of the method practical (8).

If such a complete community survey could be conducted annually, most cases of tuberculosis would be discovered and segregated relatively early. Morbidity should drop considerably within a few years and it would seem reasonable to hope that within perhaps thirty years tuberculosis would be a negligible problem. The cost would no doubt be considerably less than the enormous sums spent to control typhoid fever by insuring uncontaminated water supplies.

#### SUMMARY

1 The results of a complete community survey for tuberculosis are presented.

2 In the future, use of fluorographic methods may make such surveys cheaper and therefore more practical.

3 The possibility of eventual eradication of tuberculosis by more extensive use of the community survey is suggested.

We wish to thank Dr C A Scherer, St. Louis County Health Officer, and his staff for cooperation and assistance, and the St. Louis County Tuberculosis and Public Health Association for the financial aid which made this survey possible. We are grateful to Dr H E Hilleboe, Medical Coordinator of the Minnesota State Department of Social Security, for assistance in tabulation and analysis of statistical data.

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# THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS OF TUBERCULOSIS

VOLUME XLIV

JULY, 1941

ABST No 1

## CONTENTS

	Pages
Treatment	
d <i>Surgical (concluded)</i>	1- 2
e <i>Suction Drainage of Cavities</i>	3- 8
Tuberculosis in Animals	8-11
Diseases Other than Tuberculosis	
a <i>Nontuberculous Infections of Lungs</i>	11-17
b <i>Tumors of Lungs</i>	17-21
c <i>Pneumonoconiosis</i>	22-27
d <i>Miscellaneous Diseases of Lungs</i>	28-37
e <i>Extrapulmonary Conditions</i>	38-40

**Interposition of Colon**—Interposition of the colon between the liver and the right hemidiaphragm has been noted, and four instances, following operative paralysis of the right phrenic nerve, have been reported since 1934. Three additional cases are reported in which right hemidiaphragmatic paralysis cannot be disregarded. Symptomatology is usually not very serious and it is possible that part of the symptoms may be referable to displacement of other abdominal viscera. Symptoms are most often pain, frequently located in the chest, constipation or even recurrent obstipation. The possibility of gastrointestinal disturbance must be balanced with possible beneficial effects when considering phrenic operations for any particular case.—*Interposition of Colon following Right Phrenic Nerve Interruption*, C Muschenheim & J B Amberson, Jr, *J Thoracic Surg*, August, 1939, 8 638—(L F B)

**Phrenic Crushing**—The phrenic nerve is crushed for approximately one centimetre and then drawn upward into the neck for three and a half to four centimetres. The object is to tear any filaments entering the phrenic

nerve below the clavicle. Complete paralysis has been obtained in all of 246 patients. Paralysis remains an average of ten to twelve months. Diaphragmatic motion then begins although the diaphragm is still elevated. The diaphragm returns to its normal position two to three months after motion returns.—*A New Technique for Phrenic Crush*, L W Frank, *J Thoracic Surg*, August, 1939, 8 644—(L F B)

**Phrenic Paralysis**—One hundred and forty-one patients were operated on after seven months' observation. In 109 cases phrenic operation was the only collapse treatment, 22 per cent of the 109 patients were clinically healed and another 26.6 per cent improved. Forty per cent of the 109 became sputum-negative for tubercle bacilli. Twenty-seven per cent were fit for work after observation periods of one to seven years. Temporary phrenic operations seemed inferior. The author concludes that the phrenic operation has a decided though limited place in surgical treatment of pulmonary tuberculosis.—*Experiences and Results of Phrenic Nerve Operations Performed after Certain Observation Periods*, B O

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 ANDREWS, NEIL C., 74:874-881; 77:62-72; 78:839-847  
 ANDRUS, PAUL M., 62:170-175  
 ANGEL, R. W., 71:889-891  
 ANGELL, FRANKLIN L., 61:747-750  
 ANGEVINE, D. MURRAY, 68:657-677  
 ANGHELI, B., 79:522-524  
 ANGRIST, ALFRED A., 73:110-116  
 ANGUS, DARREL C., 70:166-170  
 ANNO, HISATO, 71:333-348  
 ANTHONY, ELEANOR, 70:1030-1041  
 AOYAMA, K., 67:545-546  
 AQUINAS, MARY (SISTER), 76:215-224  
 ARANY, L. S., 61:881-882; 74:807; 78:632  
 ARMADA, ORLANDO, 68:874-884  
 ARMSTRONG, A. RILEY, 70:907-909; 75:338-339  
 ARMSTRONG, B. W., 71:249-259  
 ARMSTRONG, FRANK L., 68:238-248; 71:193-200; 72:242-244; 73:776-778; 77:413-417  
 ARONSOHN, M. H., 69:26-36; 1057-1058; 70:1042-1053; 75:41-52; 461-468  
 ARONSON, CHARLOTTE FERGUSON, 68:713-726  
 ARONSON, DAVID L., 79:83-86  
 ARONSON, JOSEPH D., 62:408-417; 63:121-139; 717; 68:695-712; 713-726; 70:71-90; 72:35-52; 245; 74:7-14; 810-811; 79:83-86; 731-737  
 ASSELINEAU, J., 67:853-858  
 ATTINGER, ERNST O., 74:210-219; 220-228; 77:1-9; 80:38-45; 46-52; 53-58  
 ATWELL, ROBERT J., 75:846-848; 76:877-879; 880-887; 78:127-130; 399-402; 927-931  
 AUCHINCLOSS, J. HOWLAND, JR., 76:22-32; 77:863-866; 78:191-202  
 AUERBACH, OSCAR, 59:601-618; 60:604-620; 61:845-861; 62:324-330; 64:419-429; 67:173-200; 70:191-218; 527-530; 71:165-185; 72:386-389; 75:242-258; 76:988-1001; 80:207-215  
 AYVAZIAN, JOHN H., 76:1-21  
 AYVAZIAN, L. FRED, 60:305-331
- B**  
 BABCOCK, CLAUDE E., 70:109-120  
 BABIONE, ROBERT W., 62:518-524  
 BACHMAN, HENRY, 79:87-89  
 BACKERMAN, TOBEY, 69:173-191  
 BACOS, JAMES M., 67:201-211  
 BADGER, THEODORE L., 60:305-331; 65:1-23; 67:568-597; 755-778; 779-797; 74:317-342; 75:648-649  
 BAGBY, B. B., 66:436-448  
 BAI, ANGEL F., 69:554-565  
 BAISDEN, LOUIS A., 68:425-438; 439-443; 444-450  
 BALA, JOHN, 68:42-47; 71:860-866  
 BALDRIDGE, G. DOUGLAS, 63:672-673; 674-678  
 BALDWIN, EDWARD R., Bibliography, 62 (Supplement, July:114-119)  
 BALDWIN, R. W., 68:372-381  
 BALTER, ABRAHAM, M., 67:232-246; 68:782-785  
 BAN, BINDRA, 72:71-90; 76:709-810  
 BANKIER, J. D. H., 68:400-410  
 BARACH, ALVAN L., 66:778-780  
 BARBER, LOUIS M., 68:926-932; 73:882-891  
 BARBIERI, M., 72:345-355  
 BARBOUR, BLANCHE H., 77:172-176  
 BARCLAY, RALPH K., 69:957-962  
 BARCLAY, WILLIAM R., 60:385-386; 67:490-496; 68:794-795; 70:784-792; 71:556-565; 72:236-241; 713-717; 78:760-768; 79:543-544  
 BARRIST, ELLIS M., 61:735-737  
 BARRY, VINCENT C., 71:785-798; 73:219-228; 74:798-801; 75:476-487; 77:952-967; 78:62-73  
 BARSHAY, B., 68:605-614  
 BARTMANN, K., 74:475-476; 77:999-1004; 79:97-101  
 BARTON, HARRY C., 71:30-48  
 BARTZ, QUENTIN R., 63:4-6  
 BASS, H. E., 59:632-635; 60:520-523; 61:158; 62:219-222  
 BASTARRACHEA, FERNANDO, 77:473-481; 79:246-250  
 BATES, DAVID V., 80 (Supplement, July:172-178)  
 BATES, RICHARD C., 63:332-338  
 BATTAGLIA, BIAGIO, 66:594-600  
 BATTEN, JOHN, 72:851-855  
 BAUM, GEORGE L., 74:624-632  
 BAUM, GERALD L., 77:162-167  
 BAUM, LEWIS F., 59:68-75  
 BAUM, OTTO S., 59:68-75  
 BAUMGARTNER, LEONA, 79:687-689  
 BAYAN, A., 66:219-227  
 BEACHAM, EDMUND G., 66:213-218; 68:136-143  
 BEALL, GILDON N., 80:716-723  
 BEARDSLEY, FREDERICK A., 59:402-414  
 BEASLEY, CARROLL, 69:599-603  
 BEATTY, ARCH J., 62:434-438  
 BECK, CLAUDE S., 71:904-924  
 BECK, FREDERICK, 62:58-66; 66:44-51; 68:238-248; 72:151-157; 242-244; 79:134-141; 80:738-743  
 BECKER, BARNEY B., 67:22-28; 69:636-637  
 BECKER, HAROLD J., 70:806-811  
 BECKER, M. L., 76:892-895  
 BECKLAKE, MARGARET R., 76:398-409; 77:209-220; 400-412; 79:457-467  
 BEESON, PAUL B., 62:403-407  
 BEHNISCH, ROBERT, 61:1-7  
 BEKKER, J. H., 74:633-637  
 BELL, J. CARROLL, 69:71-77; 75:992-994; 995-998; 76:152-158; 683-691; 80:108-110  
 BELL, JOHN W., 73:123-127; 74:169-177; 75:538-552; 77:593-604; 78:848-861  
 BELLOW, MARJORIE, 66:666-679  
 BENNETT, RICHARD H., 62:128-143  
 BENNETT, WARREN A., 76:503-505  
 BENSON, ELLIS S., 59:415-428

to have more poultry dressed under the veterinary supervision of the State or the Federal Government. It would seem that some system could be developed whereby there might be more supervision of the handling of poultry at receiving points so that visibly diseased fowls could be rejected and destroyed at these points—*Tuberculosis, A E Night, J Am Vet M A, November, 1939, 95 611—(L F B)*

**Early Diagnosis of Bone Tuberculosis**—Pulmonary and bone tuberculosis should not be considered as separate entities but as different manifestations of the same disease. In cases where diagnosis of a bone condition is in doubt, a thorough examination of the chest should be made. Of the bones, the spine, hip and knee are most frequently involved. Pain in the spine should always be treated seriously in children because it is seldom the site of injury, and other conditions of childhood seldom cause pain. There may be a dislike of jolting or jarring the spine, as well as stiffness and tenderness. Among adults many other conditions may cause spine pain so that diagnosis is more difficult and repeated examinations by X-ray may be necessary. With hip involvement there is pain, a limp, muscle spasm, muscle wasting, and absence of real shortening. Shortening depends upon the presence of bone destruction. The same symptoms appear with disease of the knee, as well as swelling and position at which the knee is held. The slow development of tuberculosis, difficulty in interpreting X-rays and correct assessment of symptoms are difficulties in early diagnosis. Injury, infective synovitis, osteochondritis, rheumatism and "growing pains" must be distinguished from early tuberculosis. X-rays form an essential part of the examination of any bone or joint disease. Other laboratory aids in diagnosis are biopsy of the joint, removal of a regional lymph node and the Mantoux test—*The Problem of Early Diagnosis in Surgical Tuberculosis, A T Fripp, J Roy Inst Pub Health & Hyg, May, 1940, 3 127—(L F B)*

**Avian Tuberculin**—In preliminary experiments, guinea pigs infected with human tubercle bacilli were killed by intraperitoneal injection of

human as well as of avian tuberculin, animals infected with avian tubercle bacilli remained alive after injection. Animals sick with infection from human tubercle bacilli reacted positively not only to human but to avian tuberculin. Healthy animals infected with avian tubercle bacilli showed no uniform reaction to the tuberculin test. Allergy to tubercle bacilli of the human type may extend to the avian type. The presence of an infection with avian tubercle bacilli cannot be concluded on the basis of a positive reaction to avian tuberculin. Eighty-three of 100 children reacting positively to human tuberculin reacted positively to avian tuberculin. Of 18 children negative to human tuberculin 2 were found with positive reactions to avian tuberculin, without there being the slightest evidence of avian tuberculosis in them. From the high sensitivity to the heterologous antigen the conclusion is drawn that there is a close biological relationship between human and avian tuberculin and human and avian tubercle bacilli—*Untersuchungen mit Geflügeltuberkulin, K Diel & V Koszler, Beitr z Klin d Tuberk, 1939, 92 697—(R K)*

**Sensitization of Cattle by Avian Tubercle Bacillus**—Virulent avian tubercle bacilli inoculated subcutaneously have been found to sensitize cattle to mammalian tuberculin. An avirulent strain of avian tubercle bacillus was isolated from a composite of the lymph nodes of a cow from a herd with no history of bovine tuberculosis. A large dose of the culture produced acute tuberculosis in rabbits soon after its isolation but chickens inoculated with it a year later did not acquire tuberculosis. Several years after isolation the culture did not produce progressive tuberculosis in rabbits. Cultural characteristics of this strain were similar to those of virulent bacilli. Serologically, five years after isolation, the tuberculin protein from this culture cannot be distinguished from the tuberculin proteins of virulent avian tubercle bacilli. When 10 mg of the cultures of the avirulent organism was inoculated into two calves, both became sensitive to both mammalian and avian tuberculins. It was not possible to recover organisms from the lymph nodes adjacent to the point of inocu-



lation. It should be emphasized that even though bovine tuberculosis is being rapidly eradicated, cattle will continue to react to tuberculin until avian tuberculin is also eradicated. The ratio of these nonspecific reactors may be expected to continue to increase until a more concerted effort is made to eradicate avian tuberculosis from chickens and hogs—*The Sensitization of Cattle to Mammalian Tuberculin by an Virulent Strain ofavian Tubercle Bacillus*, Janet R. McCarter, L. G. Hastings & B. L. Bech, *J. Am. Vet. Med. A.*, January, 1940, 96: 52—(L. I. B.)

**Acid-fast Bacterium in Swine**—Acid fast microorganisms other than tubercle bacilli have been isolated frequently from many sources. Those recovered from animal tissues are of particular interest because of the tinctorial similarity to the tubercle bacillus and because of the possibility that they may sensitize animals to tuberculin. The microorganism reported in this study is a rapidly growing acid fast bacillus which was frequently encountered in swine that were being examined for the presence of tubercle bacilli. One tonsil was removed from each of 47 swine carcasses which at necropsy revealed slight localized lesions of tuberculosis. A similar number of tonsils were obtained from swine carcasses without gross evidence of tuberculosis. Thirteen or 27.6 per cent of the 47 tonsils from swine with slight localized lesions of tuberculosis yielded a rapidly growing acid fast bacterium. Cultures of 11 or 23.4 per cent of the 47 tonsils of swine without lesions of tuberculosis gave the same microorganism. All the cultures isolated were found to be alike in appearance and growth requirements. The microorganism apparently produces no recognizable disease in chickens, mice or calves. Subcutaneous injections of large doses in guinea pigs and rabbits will produce a localized region of caseation necrosis with no tendency toward extension of the lesion. The microorganism will sensitize guinea pigs to avian tuberculin and to homologous culture filtrates. No sensitivity to mammalian tuberculin is produced. Cross agglutination reactions indicate that the swine tonsil microorganism has antigenic components in common with the avian tubercle bacillus.

The authors have been unable to find in the literature a description of a similar microorganism—*Studies of an Acid Fast Bacterium Frequently Present in Tonsillar Tissue of Swine*, L. G. Karlise & W. H. Feldman, *J. Bact.*, April, 1940, 39: 161—(L. G. P.)

**Tubercle Bacilli in Swine Tonsils**—By bacteriological means one tonsil from each of 94 swine carcasses was examined for tubercle bacilli. Tuberculous lesions were present in the contiguous lymph nodes of 12 of the carcasses while in the remainder no lesions were found. A portion of each tonsil was removed for histological examination, duplicate sections being stained with hematoxylin and eosin and with a carboluchin combination. The remaining portion of each tonsil was emulsified, treated with 5 per cent oxalic acid and, after centrifugation, planted on glycerinated and nonglycerinated egg yolk agar media. Animal pathogenicity tests included the injection of 2 guinea pigs and 2 rabbits. Microscopically, morbid changes were present in practically all tonsils, most of minimal severity and of nonspecific character. In only 4 of the 22 tonsils from which tubercle bacilli were demonstrated were there lesions that possibly resembled tuberculosis. Bacteriologically, tubercle bacilli were obtained from 22 tonsils, or approximately 23.4 per cent of the 94 studied. Tubercle bacilli were obtained from 14 of the 47 carcasses showing gross lesions of tuberculosis and from 8 of the 47 with no gross signs of tuberculosis. Avian tubercle bacilli were found in all of the 22 cases. Naturally acquired tuberculosis in swine is practically always by way of the alimentary tract and it is difficult to understand why the tonsils are not more frequently and more seriously affected. No lesions typical or characteristic of tuberculosis were found in any of the tonsils microscopically although in 4 of the 22 there were lesions that were suggestive. Unless the practice of animal pathogenicity tests is followed a diagnosis of tuberculosis of the tonsils based on gross or microscopical appearance is only presumptive—*Avian Tubercle Bacilli in Tonsils of Swine*, W. H. Feldman & L. G. Karlise,

*J Am Vet M A*, February, 1940, 96 146 —(L F B)

**Tuberculin Reaction and Bang's Disease** — To find whether infection with *Brucella abortus* sensitizes any considerable number of cattle to tuberculin and is partially responsible for the large number of "no-visible-lesion" tuberculin-reacting cattle in Wisconsin, sera from tuberculin-reacting cattle were tested for agglutinins of *Br abortus*. The results were correlated with autopsy findings. Such tests were conducted on 805 animals. Thirteen per cent of the cattle showing tuberculous lesions also showed agglutinins for *Br abortus*, 3.1 per cent of cattle with skin lesions only had such agglutinins and 5.6 per cent of cattle having no visible lesion but were tuberculin positive showed agglutinins for *Br abortus*. Since the percentage of animals with a positive agglutination test was higher in the lesion than in the "no-visible-lesion" group, the probabilities were that few, if any, of the tuberculin reactions in the latter group were due to non-specific sensitization by *Br abortus*. Intracutaneous tuberculin tests were made on three herds of cattle experimentally infected with *Br abortus*. The conclusion, from the data obtained, would again be that cattle are not sensitized to tuberculin by abortion bacilli. The indications are that no significant number, if any, of the "no-visible-lesion" cattle in Wisconsin have reacted to tuberculin because of infection with *Br abortus*. —*Tuberculin Reactions in Cattle Affected with Bang's Disease*, E G Hastings, Janet R McCarter, B A Beach, W Wisnucky & J S Healy, *J Am Vet M A*, February, 1940, 96 186 —(L F B)

**Transitory Lung Infiltrations** —The report covers 20 patients in whom, roentgenologically, infiltrations in the lungs and symptoms suspicious of tuberculosis had been found. The infiltrations disappeared within a few weeks. It is difficult to decide whether an infiltration is of tuberculous or nonspecific origin, but generally the differential diagnosis can be made by a thorough examination. The X-ray examination is of greatest importance. The infiltrations are not tuberculous if they are

situated more centrally and appear irregularly spotted and striped with clearer areas between. In 12 of these 20 patients the infiltrations were nonspecific, in 6 tuberculous and in 2 a diagnosis could not definitely be made. If we remember that infiltrations in the lungs can also be nonspecific we will find them more often. —*Beitrag zur Kenntnis flüchtiger Verschattungen der Lungen*, G Martens, *Ztschr f Tuberk*, December, 1939, 84 26 —(G C L)

**Lung Abscess** —Seventy-seven cases of nonmalignant lung abscess are analyzed. Two-thirds of these were putrid. The routine treatment was primarily medical, surgery being employed when medical treatment failed or complications such as empyema occurred. The total mortality was 28.5 per cent. Late results are given in 43 cases. —*A Review of Seventy-seven Consecutive Cases of Pulmonary Abscess*, A G Bryce, *Brit J Tuberc*, October, 1939, 33 197 —(A P)

**Lung Abscess** —The absence of symptoms and the disappearance of the roentgenographic findings of a lung abscess and its surrounding pneumonitis are usually accepted as evidence that an abscess has healed. However, the number of recurrences reported suggest that these criteria are insufficient. For many years bronchography has been used to determine the effectiveness of thoracoplasties in the closure of cavities, to demonstrate both tuberculous and nontuberculous bronchiectasis, and to study the various phases of lung abscess, but there is no account in the literature of such routine studies in apparently healed abscesses. Amberson *et al* quite regularly demonstrated residual cavities or bronchiectasis in cases of apparently healed abscess with bronchography, but have not reported their work. Therefore, a group of 6 cases of lung abscess are reported and the results of bronchographic study presented. In all these cases the abscesses were considered healed according to the usual criteria, but bronchograms showed either bronchiectatic defects or remnants of cavities. The latter probably represents an arrested stage of the fibrotic contraction of the cavity and should be regarded as less than theoretically complete healing. Such *residua* are not

as common as bronchiectasis. The bronchiectatic remnant is explained by Pinner's concept of the unity of bronchopulmonary suppuration. He demonstrated that all phases of bronchopulmonary suppuration are present in some degree in bronchopulmonary suppurative lesions, the predominance of one phase determining the clinical diagnosis. The permanence of bronchiectasis is well known and the tendency to reactivation has been reported by many. Reports of cure are probably based largely on the disappearance of symptoms rather than the disappearance of bronchiectasis. It seems logical, therefore, to regard bronchiectatic residues from lung abscesses as potentially dangerous. It is believed that bronchographic study should be employed routinely to determine the state of bronchi and lung after the symptoms and roentgenographic shadows of acute suppurative pulmonary disease have disappeared.—*Bronchographic Study of Apparently Healed Lung Abscesses*, R. M. Franklin, *Am. J. M. Sc.*, July, 1939, 198-95—(G. F. M.)

**Lung Abscess**—Viswanathan cites Maxwell's classification, primarily an anatomical one. Of 32 cases in his series 26 were unilocular, 24 peripheral and 30 communicating with a bronchus. In 10 cases an upper lobe was involved and one was definitely apical. The commonest age group was thirty to thirty-nine. There were 26 males and 6 females. It is thought that many cases result from an abortive pneumonia in pneumonitis and Scadding's disseminated focal pneumonia. In 20, the onset was sudden, in 8 insidious. Fever was the commonest initial symptom, usually preceding cough by about two weeks. In 26 there was purulent sputum and in 22 it was foul. Haemoptysis occurred in 16 but was the initial symptom only once. Four patients showed clubbing of fingers. A dull continuous chest pain was common, differing from ordinary pleurisy. Physical signs were variable and occasionally absent. Feeble breath sounds and diminished vocal resonance were as common as the typical cavity signs. In 6 cases the roentgenographic evidence was completely decisive, in the others confirmatory. Rapidly spreading changes suggest pulmonary gangrene.

Surgical drainage was used in 10 with 5 deaths. Pneumothorax was given in 1 with one death. Medical treatment was tried in 18 of whom 5 completely recovered, 3 left prematurely, 3 left on unsound advice and 7 died. It is generally agreed that medical treatment is the choice in the early stages. Re- and postural drainage are the first measures. The oral and sulphonamide group of drugs and intravenous penicillin have been used. In suitable cases bronchoscopic drainage and aspiration are effective. If there is not marked improvement after six weeks' medical treatment, surgical drainage is indicated. Artificial pneumothorax is successful in a small percentage, not near the periphery and with free bronchial communication. A series of roentgenographic reproductions accompanies the paper.—*Abscess of the Lung*, R. Viswanathan, *Tubercle*, March, 1939, 20-26—(1 P)

**Lung Abscess**—An analysis is presented of 88 cases of lung abscess, of these 57 per cent are well or improved and 31 per cent dead. Abscesses developing as complications of lung tumors or those originating from a long standing bronchiectasis were excluded, also all cases complicated by tuberculosis or resulting from a generalized septicæmia. However, no attempt was made to separate the cases of pulmonary gangrene from those of abscess, for it seems that no clear cut dividing line can be drawn between them in the majority of instances. There were 58 males and 30 females in the group and all but 5 were adults. Although lung abscesses usually occur in the lower lobes, in the present series the upper lobes were found more frequently involved than the lower. The importance of respiratory infections, such as pneumonia, in the aetiology of this disease was noted in the group, 40 per cent gave a history of pneumonia. Other conditions found to be factors in the production of abscess were operations on the upper respiratory tract, especially tonsillectomy and operations in other parts of the body, mainly abdominal. In quite a large group the precipitating factors were unknown. In cases following tonsillectomy and other operations on the upper respiratory tract, the evidence favors aspiration of infected material as the most likely

cause Probably the most important single step in the pathogenesis of the majority of lung abscesses, however, is atelectasis This may follow the plugging of a bronchus or bronchi, it may occur in the course of pneumonia if bronchi are plugged by tenacious exudate, it may follow the aspiration of vomitus or a foreign body The bacterial flora of the cases studied varied *Streptococcus viridans* was very prominent in the sputum, it was at times aerobic and at other times facultatively anaerobic However, anaerobic streptococci and Gram negative bacilli were the organisms most frequently found in the abscess itself Fusiform bacilli and spirochaetes in significant numbers were found in about one quarter of the cases, these organisms apparently playing a secondary rôle The symptoms and signs in these cases presented nothing unusual Cough was generally the earliest symptom and chest pain occurred frequently The sputum was usually profuse and frequently offensive, but not always so Gross haemoptyses were not uncommon The pulmonary signs were very meager in many patients, the most common signs were dulness (43 per cent) and râles (40 per cent) The chief reliance for demonstrating the abscess proved to be the X-ray and frequently multiple films and positions were necessary The most important X-ray change during the evolution of the abscess is at first an ill defined area of increased density which later becomes sharply demarcated, and in which there may finally develop a cavity with a fluid level Care must be taken not to confuse the findings with tuberculosis or carcinoma Bronchiectasis, with secondary abscess, is best differentiated by the long history and by lipiodol study The importance of prophylaxis is stressed This concerns itself mainly with eradication of infections in the nose, throat and mouth especially before operation The type and depth of anaesthesia and the position of the patient during the operation are important The aspiration of secretions from the trachea during and after operations and inhalations of carbon dioxide are frequently necessary When the disease is established the general methods useful in combating any prolonged infection apply, and the patient should have a carefully supervised course of postural

drainage Steam-inhalations and ammonium chloride by mouth may make the secretions less viscid Routine bronchoscopy is a very important step for localization of the abscess and may promote better bronchial drainage by permitting the sucking out of plugs of mucus and pus and the cauterizing of obstructive granulations Arsenicals were not used routinely but only where spirochaetes and fusiform bacilli were numerous There were 13 such cases The mainstay of the medical treatment was, however, postural drainage and this was made as nearly continuous as possible Surgical treatment is often withheld too long This should be considered when a patient fails to show improvement after three to five weeks of conservative treatment, though the interval will vary from case to case The trend now is toward earlier operations, but it should not be so early that the patient is not given a good chance for recovery under a medical regimen The aim of surgical treatment should be to provide adequate drainage without contaminating the pleural cavity This can usually be accomplished safely and efficiently by a two-stage operation, using the actual cautery for incision into the abscess Chronic abscesses are more difficult to cure than early ones, hence the longer the duration prior to treatment the less favorable the prognosis Multiple abscesses are also difficult to treat as are those complicated by pre- or post-operative haemorrhage and chronic alcoholism Of the 50 successful results, 32 received medical treatment and 18 surgical treatment Of the 38 unsuccessful cases, 25 received surgical treatment Twelve of these had a preliminary course of medical treatment, however The earlier treatment is instituted and the more carefully prophylactic measures are observed the better the results will be in curing and preventing this disease—*Lung Abscess, Analysis of 88 Cases, A M Fisher & G G Finney, Bull Johns Hopkins Hosp, May, 1940, 66 263—(J S W)*

**Chronic Pneumonitis**—The authors define chronic pneumonitis as an infectious process of the lung leading to sclerosis with or without formation of bronchiectasis and cavities The conception of pneumonitis includes not only

chronic suppuration of the lung, but abscess, gangrene and other pathological conditions. The pneumococcus is present in 80 or 90 per cent of cases, and the streptococcus, staphylococcus and Friedländer's pneumobacillus may occur. Among the symptoms described are moderate cough, frequent or paroxysmal, with expectoration, which may be mucous, mucopurulent, bloody or foul. Fever, anorexia and anemia reflect the constitution it damage. Clubbed fingernails and cyanosis may appear early. Pain reveals involvement of the pleura. Physical examination shows diminution of thoracic elasticity, atrophy, muscular contraction and alteration of the breath sounds. The following processes are able to produce chronic pneumonitis: lobar pneumonia, lobular bronchitis pneumonia, lipoid pneumonia, infected atelectasis, abscess, the suppuration of cancer, hydatid cyst, pneumoconiosis, syphilitic pneumonia, pneumomycosis and pneumonia from war gas.—*El concepto actual de las neumonitis crónicas*, M. Celaya & I. Olcun, *Rev. Med. Lat. Am.*, August, 1937, no 24, 1087—(E. C. I.)

**Pneumonia**—Pneumococcus pneumonia in the U. S. A. is incomparably more frequent and serious than in France. Studies of fundamental importance were carried out by Bullowa and Greenbaum at the Harlem Hospital in New York City, by Finland and his collaborators in Boston and by Corvillo and Birnbaum of New York City. Acute lobar pneumonia has in the U. S. A. an average mortality of 30 per cent. The gravity of the illness has stimulated considerable laboratory research on the pneumococcus. Pneumococcus pneumonia takes three clinical forms: lobar, atypical and bronchopneumonic. The onset is usually a tracheobronchitis, gripe or a "simple cold in the head." Finland states that atelectasis is a frequent complication of primary lobar pneumonia which explains certain unusual physical signs and occurrences in the clinical course. Certain episodes of acute dyspnoea or even sudden death may be provoked by atelectasis in the course of pneumonia. At the Boston City Hospital, 62 cases of pneumonia with atelectasis have been observed between 1929 and 1936, and 47 of these have

shown atelectasis of varying degrees at autopsy. Corvillo explained the mechanism of atelectasis by complete obstruction of a bronchus, the alveolar gases being absorbed by the blood stream. Experimentally, Corvillo produced both atelectasis and lobar pneumonia in dog by an inoculation of virulent pneumonic sputum. In the new born, atelectasis and pneumonia are provoked by obstruction of a bronchus by amniotic fluid or by epidermal cells. From a therapeutic aspect it is most important to identify the particular type of pneumococcus. Finland states that there are 33 types. In order of frequency they are types 1, 2, 3, 8, 6, 5. In infants the order of frequency is 1, 6, 11, 19, 3, 4, 7. The treatment used is anti pneumococcus serum of the horse. Finland uses intravenous injection of serum. Bullowa uses intramuscular injection in early cases. Contraindications to serum include very grave illness, asthmatic, though not desensitized to horse serum, the very old and those with other organic diseases. Oxygen is used for anoxemia. To prevent bronchial obstruction the patient lies on the healthy side. Hospitals in the U. S. A. are well organized to handle pneumonia. In the U. S. pneumonia ranks third, but in France it is much less common.—*Traité et des pneumocoques pathogènes d'après les travaux américains récents*, O. Monod, *Arch. néd. clin. de l'app. respir.*, 1938, 13 no 6, 466—(J. E. F.)

**Pneumonia**—In January 1939 an epidemic of a mild disease of the respiratory tract occurred in Philadelphia, this reached wide-spread proportions in February. Similar outbreaks were reported in other cities. Since most patients were not ill enough to seek medical aid, it was not possible to learn the true extent of this pandemic. Clinically, these cases were similar to a series of patients with atypical pneumonia reported in 1938. In two cases of the latter group, a filterable virus, different from the influenza virus, was isolated. In the 1939 epidemic, at the Jefferson Medical College and Hospital, there were 407 cases, among the internes, nurses and medical students. Only about 100 were ill enough to be admitted to the hospital. The period of incubation was uncertain. The disease was primarily an in-

inflammation of the mucous membranes of the respiratory tract, usually of the nose, pharynx and larynx, occasionally including the trachea and bronchi, and in a few cases the bronchioles and lungs. Constitutional symptoms were usually in proportion to the extent and intensity of the mucosal lesions. The clinical course was remarkably uniform in most cases, differing chiefly in severity. The patients were classified as mild (ambulatory), moderately severe and severe. Seventy-five per cent were mild. These cases would ordinarily be regarded as colds but because of their coincidence with more severe, but clinically similar, infections they were regarded as part of an epidemic of a single disease entity. The symptoms were referable to inflammation of the upper respiratory tract. There was occasional dry cough but rarely fever. The illness lasted from one to several days. About 100, or 25 per cent, were sick enough to go to bed. Of this number, 25 had tracheobronchitis and 25 had tracheobronchopneumonia. The onset in most cases, as in the mild form, was insidious. Over 70 per cent of this group had persistent hacking cough. Only 27 raised sputum, but never more than 30 cc a day. The chief symptoms were anorexia, muscular soreness from coughing, vomiting and diarrhoea. Fever lasted on an average two and a half days in patients without involvement of the lungs, four and six-tenths days in those with tracheobronchitis and eight and two-tenths days in those with pneumonia. The temperature usually ranged between 101° and 103°F. The sputum, when present, was not characteristic and was occasionally blood tinged. The leucocytes ranged between 5,000 and 8,000, often with a slight increase in proportion of the polymorphonuclear cells. In 25 patients who developed pneumonia, the onset was insidious and signs of spread to the lungs appeared after several days. Fever was continuously high or occasionally remittent and the temperature declined by lysis. The disease with pneumonia lasted from two to seventeen days, with an average of eight and two-tenths days. All blood cultures were sterile. In a number of cases relapse, with mild nasopharyngitis, occurred after several weeks. The number of leucocytes was usu-

ally normal or slightly increased toward the end of the illness. Three patients developed jaundice five to seven days after the beginning of symptoms of nasopharyngitis, the clinical course was then typical of catarrhal jaundice. In 5 cases, after several days of the mild symptoms, typical acute follicular tonsillitis with leucocytosis developed. Aside from demonstrating the absence of the influenza virus, aetiological studies gave no decisive results. Various bacteria were grown but none was considered to be of aetiological importance. There was a remarkable scarcity of pneumococci. Treatment was symptomatic. Sulfapyridine and serum were tried in a few of the patients with pneumococci in the sputum, but the absence of a prompt response suggested that the pneumococci were of no aetiological significance. This epidemic disease is considered to be a clinical entity similar to epidemic influenza but caused by a different agent. There were no deaths in the entire series. The disease should be given a temporary general name, such as grippé, as differentiated from true influenza, until the aetiological agent is discovered. This agent is most probably a filterable virus—*An Epidemic Disease of the Respiratory Tract*, H A Reimann & W P Havens, *Arch Int Med*, January, 1940, 65 138—(H R N)

**Pulmonary Lues**—Although this disease was first suspected by Paracelsus early in the sixteenth century, it was recognized as a clinical entity only within the last century, mainly through the exhaustive study of Virchow. Later, following the discovery of the bacillus of Koch, there was doubt regarding many diagnoses of pulmonary lues, and tubercle bacilli were found in the sputum of several of these cases. Some investigators believed that tuberculosis was superimposed upon the luetic process in the lungs, thus creating a confusion of the two conditions. When Schaudinn discovered the spirochaeta many clinical pictures appeared to have been cleared, but Koch and others threw doubt on the theory that the spirochaeta often found in pulmonary lesions was specific. Contemporary opinion as to the incidence of pulmonary lues varies, observers have found it at au-

topsy in from 1 per cent to 10 per cent of luetics. It is more frequently considered a complication of hereditary lues, showing a predilection for the midzone and the lower third of the lung, predominantly on the right, it occurs more often in men than in women, and in the age group, forty to fifty years. When pulmonary lues develops in a tuberculous lung, it often reveals latent lesions and increases their activity. On the other hand when pulmonary tuberculosis develops during the primary or secondary stage of lues, it assumes an exudative form, while during tertiary lues it frequently appears as pulmonary fibrosis. A complete case report is given of a fifty-eight year old woman in whom advanced pulmonary tuberculosis was diagnosed. Death occurred after a few days of observation from cardiac failure. At autopsy a hypertrophic heart and diffuse fibrosis of the right lower lobe were discovered. Histology apparently demonstrated pulmonary lues. Syphilis of the lung, though rare, should not be so difficult to diagnose, as many still claim. Anatomohistological examination without doubt affords all the necessary information for diagnosis, as well as for the differentiation of this process from others — *La sifilide del polmone*, V Agnello, *Lotta contro la tuberc*, June, 1939, 10 512 —(S L)

**Pulmonary Actinomycosis** —The authors report a forty-three year old white mechanic with fever, cough, chest pain, loss of weight and fatigue. Three physicians who examined him made a diagnosis of right basal pleurisy. Aspiration yielded bloody, purulent fluid. Radiological examination showed an obliterating pleuritis in the base of the right lung. Sputum examination was negative for tubercle bacilli on several occasions. Bronchoscopic aspiration showed normal bronchial mucosa. Bronchography demonstrated the pleural lesion. A month later a tumor with the characteristics of anthrax appeared in the lower lateral region of the right thorax, aspiration of which yielded negative results. Several bacteriological examinations were made, and also culture on Sabouraud's medium, with negative results. The patient became gradually worse and the lesion grew in size. Finally examination showed the presence of the ac-

tinomyces in the evacuated pus — *Actinomycosis pleuro pulmonar simulando en su comienzo una tuberculosis pulmonar*, V Martinez & F Dominicz, *Rev de tuberc*, January, 1939, 1 33 —(E C I)

**Bronchitis** —Eosinophilic catarrh of the bronchi is in no way identical with asthma. This syndrome arises in so-called allergic constitutions and is clearly to be differentiated from asthma. There are eosinophiles in the sputum but not always in the blood. A certain relationship to tuberculosis is probably present but not always easily proven. In *bronchitis mucinosa* or *fibrinosa plastica* bronchial casts are often coughed up, which can be recognized as ramifications of the bronchi to the finest bronchioles. Constitutional make-up plays an aetiological rôle in this form also. Bronchial spirochaetosis is caused by the *Spirochaeta Castellani* and is recognizable immediately on examination of the sputum. The spirochaetes, longer and thicker than *Spirochaeta pallidum*, are demonstrable with gentian violet and by Romanovsky method. The therapy is the same as for other spirochaetal bronchitides, namely neosalvarsan — *Über seltene Bronchialerkrankungen*, G Schroder, *Deutsches Tuberk -Bl*, March, 1939, 13 61 —(R K)

**Infectious-Allergic Bronchitis** —In 4 members of a family an infectious-allergic bronchitis with eosinophilia and loud rales was observed. The cause of this disease could not be revealed — *Eine eigerartige infektiös-allergische Bronchitis*, P G Schmidt, *Ztschr f Tuberk*, January, 1940, 84 155 —(G C L)

**Congenital Bronchiectasis** —From the casuistics of 66 of the author's cases and from reports in recent literature the arguments for the congenital nature of bronchiectasis are discussed. The frequency of the simultaneous existence of malformations or anomalies and bronchiectasis, as well as the frequency of its familial incidence and of its occurrence in identical twins, support earlier observers' conception of its congenital nature. The coincidence which is relatively frequently observed between bronchial asthma and bronchiectasis

is possibly explained by a bacterial allergy in the bronchiectatic patient. Observations on the incidence of chronic sinusitis in patients with bronchiectasis show striking agreement with the results which Kartagener's clinic reported earlier. The same also holds in relation to the size of the frontal sinus, which is considered to be an indicator of the importance of a constitutional factor in the aetiology of bronchiectasis — *Erfahrungen an weiteren Bronchiektasie-Patienten*, J Hasler, *Beitr z Klin d Tuberk*, 1939, 93 630 — (R K)

**Aspergillosis in a Skunk** — Aspergillosis in the lungs has been reported in practically all domestic animals, including dogs, and has been frequently reported in all the avian families in Europe and the United States. The authors report its appearance in a skunk. A cat was persuaded to serve as foster mother for 5 orphaned baby skunks. When about one month old they were operated upon for removal of the scent glands. The wounds healed well in all but one. Ten days after the operation this animal died. A dirty-gray diarrhoea was present and autopsy revealed all organs normal except the lungs. In the lungs there was a marked greenish discoloration with haemorrhage in the marginal areas of all the lobes, the alveoli were filled with a greenish watery fluid, and the primary and secondary bronchi showed catarrhal inflammation and a mucous exudate of greenish color. Mycelia of the mould could be demonstrated with cover-slip preparation and was identified as *Aspergillus fumigatus*. The animals had been kept in a basement with a concrete floor. The floor was damp and a mouldy grain was found on the floor which apparently was the source of the infection — *Pulmonary Aspergillosis in a Skunk*, A J Durant & E R Doll, *J Am Vet M A*, November, 1939, 95 645 — (L F B)

**Cancer of Lung** — In order to determine the effect of roentgen therapy on the histological picture of lung carcinoma, 21 patients who had received roentgen therapy and 64 non-irradiated patients, used as controls, were studied postmortem. Five irradiated metastatic lesions from carcinoma of the lung were

also studied. All the cases, with two exceptions, were treated with 200 kv. Most of them were treated with 25 ma. with a few exceptions in which 5 and 10 ma. were used. The primary tumors were usually treated by using three 15 by 15 cm. thoracic portals, located anteriorly, posteriorly and laterally. In general, the histological changes produced by roentgen therapy were degenerative in the acute stage and retrogressive in the later stages, accompanied in some cases by profound alterations in cell type. Among the 64 nonirradiated controls many instances of degenerative and retrogressive changes were seen which resembled those observed in the radiated cases, yet the total pictures were different. In evaluating the changes seen in irradiated tumors, some reliance was placed on the comparative appearance of their metastases and on biopsy sections secured prior to therapy. The most acute changes consisted of intercellular and intracellular oedema, vacuolation of cytoplasm with an increased affinity for acid dyes and some actual cell necrosis. The later stages were those of disorganization of the architecture of the tumor and alteration of cell type. Frequently, adenocarcinomata lost their ductal or tubular appearance and became more undifferentiated and in squamous cell carcinomata the arrangement of cells into squamous epithelium-like layers was lost. The cellular changes following irradiation were those of anaplasia or increase in undifferentiation, rather than metaplasia. The cells became enlarged, some reaching giant size. The nuclei became more chromatic and were sometimes pyknotic. The nuclei tended to be enlarged, and multiple nuclei, ring nuclei and eccentrically placed nuclei were common phenomena. In the later stages there was also an increase of fibrous connective tissue in the tumor. In none of the 21 cases, in which doses up to 5000 r were used, was there complete destruction of the tumor. The smallest dose which produced visible damage was 1490 r, but the carcinocidal dose is probably above 5000 r. Study of 5 irradiated metastases revealed one skull lesion which appeared to have been completely destroyed by a dose of 3800 r, there was no effect on the other 4 metastases. Study of the tissues and organs adjacent to the



irradiated tumor revealed no changes aside from those usually seen in the skin following radiotherapy. Squamous cell carcinomata and adenocarcinomata were more radiosensitive than the undifferentiated carcinomata which, contrary to expectation, were either highly radioresistant or highly radiorecuperative. The average period of survival after the onset of symptoms in the 53 nonirradiated controls, where data were available, was 10.5 months. The 21 patients treated with roentgen rays survived for an average of 11.9 months after onset of symptoms. Careful study of the individual cases reveals that even this slight difference in survival time is only apparent, and that roentgen therapy in this series had no beneficial effect—*Effects of Roentgen Therapy on Histologic Picture and on Survival in Cases of Primary Carcinoma of Lung*, P. Steiner, *Arch. Int. Med.*, July, 1940, 66: 140—(H. R. N.)

**Cancer of Lung**—The observations are based on 88 cases. In 68 cases there was histological proof of the diagnosis of pulmonary carcinoma, in the remaining 20, there was strong clinical and roentgenological evidence. Weight loss is a common symptom, loss of 20 pounds or more usually signifies the presence of abdominal metastases. Chronic hoarseness, found in 10 per cent of this group, almost always signifies envelopment of the laryngeal nerve by the tumor mass. Haemorrhagic pleural effusion is almost pathognomonic of malignant neoplasm. The most essential factor in the development and variability of the X-ray picture is the degree of bronchial occlusion. This determines the degree of secondary atelectasis and the amount of secondary abscess formation. Primary interest centered in the effect of roentgen therapy which was employed in 42 patients in this group. The dose ranged from about 1,200 to 16,000 r. There has been increasing recognition of the inefficacy of weak irradiation and the higher dosage has been used to a greater degree. Duration of life after the onset of symptoms in the patients who were treated was about the same as in the untreated patients. As a curative treatment, roentgen therapy was a complete failure. There may be an effect in the form of some symptomatic relief

which is caused by a release of bronchial occlusion and clearing of atelectasis following some shrinkage of the tumor. Three patients reported disappearance of symptoms following roentgen therapy. However, this occasionally occurs without any therapy. Any roentgenographic changes which follow roentgen therapy seem to be due to clearing of the atelectatic area rather than to any real destruction of the tumor. Radiation sickness in the form of nausea, abdominal distress, severe headaches and general weakness was frequent in this series. Anaemia develops and transfusions have to be employed. The patient with hopeless pulmonary cancer dies an easier death without treatment. The literature offers no unequivocal example of cure of pulmonary cancer by roentgen therapy. Duration of life following diagnosis may be considerable without any treatment. The authors do not wish to discourage further work in the field of roentgen therapy in this disease. At present, the surgical removal of operable tumors must be the treatment of choice—*Bronchogenic Carcinoma*, R. Bloch & G. Bogardus, *Arch. Int. Med.*, July, 1940, 66: 39—(H. R. N.)

**Cancer of Lung**—The early recognition of bronchogenic carcinoma has not kept pace with the increasing realization of its frequent incidence. The authors in a study of 23 proved cases, emphasize the protean manifestations of this condition in part explanation of the failure to make early diagnoses. It has apparently been established that there is a real increase in the frequency of cancer of the lung. The aetiological factors remain obscure. The relative importance of chronic inflammatory processes, inhalation of irritating substances and hereditary susceptibility have their support. The primary growth is located more frequently on the right than on the left side, according to most statistical analyses. The site of predilection is the main bronchus or its larger branches. The hilar type of lesion is the most common. The main bronchus and the bronchus to the lower lobe on each side are the favorite locations for the neoplasms. Other varieties of primary growths are described as lobular and nodular, and are found in the peripheral lung fields, varying in appearance

from a similarity to miliary distribution, or infiltrative, to nodular, and even diffusely infiltrative or pneumonic in type. Histologically squamous, adenocarcinomatous and anaplastic varieties are recognized. The squamous cell type of tumor is the most common, but the classification of a tumor must be accepted with reservations, because different sections may present different microscopical features. A common cellular origin from epithelial basal cell deposits would predispose toward pleomorphism. The primary lesion spreads by way of the peribronchial lymphatics, and peripheral tumors often simulate metastatic or pleuritic growths. Pleuritic involvement may induce effusion into the pleural cavity. Extension to the regional and mediastinal lymph nodes is common, and mediastinal tumors may attain considerable size. The tendency of bronchogenic carcinoma to cause widespread and early metastasis is well known. The situation of the lung in the circulatory system would favor generalized haematogenous dissemination. Metastatic bronchogenic carcinoma is worthy of consideration in the case of any obscure intraabdominal lesion. Secondary pathological features are common, the tumor may obstruct the bronchus by intra-bronchial growth or by invasion of the wall, producing constriction. Obstruction causes defective drainage with consequent infection. Chronic bronchiectatic, suppurative, pneumonic and pleuritic phenomena in any combination may ensue. Atelectasis may complicate the obstruction and perpetuate the infection. The average age of the 23 cases in the series was fifty-one, and all but 4 patients were males. These tumors occur at an earlier age than one generally associates with malignant growth. Hemoptysis is the chief subjective sign. In this series, hemoptysis occurred in 34 per cent of the cases. Dyspnoea occurred in 38 per cent, and was the presenting complaint twice. Pain in the chest proved severe in 8 cases, in 5 of which it was the presenting complaint. Productive cough was present in 9 cases. Hoarseness occurred in 5 patients. Thirteen per cent of the patients had no symptoms referable to the respiratory tract. In 5 cases there were presenting complaints due to a remote metastatic manifestation of the disease.

The direct roentgen sign is the presence of a fairly homogeneous shadow, well defined, usually at or near the hilum. This shadow may send extensions into the lung field. Indirectly there may be produced emphysematous or atelectatic phenomena resulting from partial bronchial obstruction. The atelectatic process is of slow development when compared to the atelectasis of foreign body origin. Mediastinal shift is greater with lesions of a lower lobe than with lesions of an upper lobe. Complete or partial collapse of the lung creates a favorable nidus for infection. Pleural fluid may be the result of extension of parenchymal infection of the lung or may be the result of pleural metastasis. In the series, there was direct roentgenographic evidence in only 6 cases. In 13 cases the presence of tumor could be inferred only from evidence of secondary pathological processes. Bronchoscopic examination should be done in all cases of obscure involvement with evidence of bronchopulmonary pathological change.—*Bronchiogenic Carcinoma A Diagnostic Enigma*, E. L. Jenkinson & A. T. Hunter, *J. A. M. A.*, December 30, 1939, 113:2392—(G. L. L.)

**Cancer of Lung**—The only adequate methods available in the fight against cancer are radium, X-rays, fulguration and surgical excision. All forms of irradiation have up to the present time failed completely as curative agents. High voltage roentgen therapy does not prolong the lives of patients with carcinoma of the lung, because the great majority of the tumors are radioresistant. The failure of irradiation is not surprising, since the administration of a dosage sufficient to destroy the tumor without irreparable damage to the surrounding tissues is practically impossible. Treatment of primary carcinoma by endobronchial fulguration is, in the opinion of the authors, practical only in extremely rare cases. The outlook for the patient is now much brighter with the introduction of surgical excision of lung tissue as a practical procedure. Its future will depend on three factors: (1) early diagnosis before metastasis has occurred, (2) a relatively low operative mortality rate, and (3) a reasonable chance of cure without excessive permanent disability. The general opinion now

is that all primary carcinomata arise from a single undifferentiated parent cell located in the basal layer of the bronchial epithelium. From a clinicopathological standpoint the symptoms and signs may be divided into several stages. (1) The stage before bronchial occlusion, characterized by irritating cough, clear, thin, mucoid sputum, with later blood streaked sputum following increase in growth and ulceration, physical manifestations and roentgenographic changes are not present during this stage. (2) The stage of bronchial occlusion, varying from partial occlusion with emphysema to complete occlusion with atelectasis and usually with secondary infection, characteristic symptoms, physical signs and roentgenographic manifestations accompany the varying degrees of bronchial occlusion. (3) The stage of extension or metastases, with its varying symptoms and signs unimportant clinically because indicative of a hopeless prognosis. In considering the effects of bronchial occlusion it is important to realize that the severity of symptoms and the prominence of changes will be directly proportional to the size of the affected bronchus. The authors present an analytical study of a series of 75 cases, all proven histologically, the ratio of men to women being 2.6 to 1. Fifty-seven lesions were located in the stem bronchus and 18 peripherally. Cough was present in 87 per cent of the entire group, fever in 53 per cent, chest pain or discomfort in 44 per cent, haemoptysis in 38 per cent and dyspnoea or wheezing in 38 per cent (frequently an early symptom). Roentgenographic changes were present in 96 per cent. Approximately three-fourths of all primary lung tumors are situated in the major bronchi, so that they can be bronchoscoped. In this series of 55 stem bronchus lesions a biopsy of tumor tissue was obtained in 53 instances. Bronchography should be used only if the results of bronchoscopy are negative. The demonstration of malignant tissue in the sputum has in a limited series of the authors' cases proved disappointing. Aspirational biopsy is a dangerous procedure, since pleural infection may follow withdrawal of a needle from an infected lung. Exploratory thoracotomy was carried out in 38 of the 75 cases in this series. Before

thoracotomy is done, one should be sure that there is no clinical evidence of metastasis. In the group of 75 cases, lung resection was carried out in 21, pneumonectomy in 17 and lobectomy in 1. Pulguration was possible in only one instance. In the final analysis there were 18 cases (24 per cent) in which no evidence of metastasis or extension of the tumor was found at the time of the operation. Of the 4 lobectomies, one is alive and well sixteen months after operation. Of 17 pneumonectomy cases, 8 are living and all with no evidence of recurrence, the longest postoperative period being five years and four months. Lobectomy and pneumonectomy are practical therapeutic procedures offering a good chance of survival and without excessive operative mortality. Bronchoscopic examination is by far the most important diagnostic procedure available and should be used without delay in any case in which symptoms suggestive of early primary carcinoma of the lung cannot be definitely explained on some other basis. — *Clinical Studies of Primary Carcinoma of the Lung in Analysis of Severe-Type Cases, Twenty-One of Which Were Treated by Pneumonectomy or Lobectomy*, R. H. Overholt & W. R. Rime, J. A. M. A., March 2, 1940, 114: 735. — (G. L. L.)

**Cancer of Lung and Subpleural Scars.** — This is a study of material obtained at autopsy from fifteen cases of carcinoma of the lung originating in the vicinity of subpleural scars. The carcinomata themselves contained anthracotic scar tissue. The scar tissue was frequently extensively hyalinized consisting of nodules containing very few cells or appeared as an agglomeration of connective tissue with hyalinization of the fibrous substance and keloid formation. In five instances cholesterol crystals were present in these scars. Occasionally the fibrous material was rich in fibroblasts. The scar was usually drawn up to the pleura by fibrous bands radiating from the tumor. In the immediate vicinity of the scar the tumor was usually necrotic leaving only a trace of the cellular proliferation. Alveolar structure was represented only by remnants of elastic tissue. In the necrotic central sections of the tumor tissue itself, cholesterol

crystals and anthracotic pigment might be present. In one instance alveolar remnants were observed in the hyaline scar. It is postulated that these cancers are "scar cancers," for the scars themselves are too old to have occurred secondary to the tumor. Support is lent to this idea by the presence of scar tissue containing coal pigment in the centre of the cancer. There arises the possibility of a relationship of tuberculous infection to these cancers. Tuberculous scars accumulate anthracotic pigment much more readily than other types of scars. In several cases there were signs of old tuberculosis in the scar itself or in other parts of the lung—*Periphere Lungenkrebsc auf dem Boden pleuranaher Narben*, G. Friedrich, *Virchows Arch*, July, 1939, 304-230—(C L D)

**Cancer of Lung**—In order to obtain further information regarding these tumors, 40 necropsies were studied. Based on morphological characteristics, these neoplasms fell into two groups: squamous cell carcinoma and cylindrical cell carcinoma. A third group, pleomorphic cell carcinoma, was added in which the tumor presented more than one cell variety. In this classification, cylindrical cell carcinoma included adenocarcinoma, and undifferentiated cell carcinoma, such as medullary, round cell and oat cell carcinoma. Two cases of the 40 showed no metastases. The greatest number of metastases occurred among the cases with adenocarcinoma. It seems evident that these different forms of tumor cells have originated from the deeper basal cell layer lining the mucosa of the bronchial tree. The basal layer of epithelium is the least differentiated and possesses the various potentialities for growth and cell differentiation. It is believed that the various epithelial growths have, in all probability, a common genetic origin and that they are all capable of responding to the same growth stimulant—*Primary (Bronchiogenic) Carcinoma of the Lung*, J. Rabinovitch, L. A. Hochberg & M. Lederer, *J Thoracic Surg*, February, 1940, 9-332—(L F B)

**Metastases of Cancer of Lung**—Forty cases of bronchogenic carcinoma are analyzed with respect to metastasis. The chief sites of

secondary growth were the anterior mediastinal and tracheobronchial lymph nodes, which were involved in 32 and 23 cases, respectively, of the series. Metastasis to the lymph nodes of the abdominal cavity was less frequent, with 6 in the mesenteric lymph nodes, 2 in the lumbar-aortic and one each in the coeliac, hepatic and pancreatic nodes. There were 10 cases of secondary growth in the supraclavicular nodes. Of the viscera, the liver was involved most frequently, viz., in 16 out of the 40 cases. The kidneys were affected in 14, the suprarenal glands in 10 and the myocardium together with the pericardium in 5 cases. Metastases to the skeletal muscles occurred in 3 cases. The ribs were the seat of secondary growth in 5 cases and the vertebral column and sternum in 2 cases each. Metastases were observed in the skin in relatively few instances. The central nervous system was not examined regularly in the series and hence figures are not given for metastases in this system—*Las metastases en los canceres bronquiales*, J. A. Jimenez & P. A. Castillo, *Arch de med int*, 1939, 5-264—(E R L)

**Pneumonectomy for Carcinoma**.—Recent autopsy studies have shown the incidence of pulmonary carcinoma to be as high as 10 per cent of all carcinomata. According to the literature, approximately 100 patients have undergone pneumonectomy for carcinoma. Six have survived five years without evidence of recurrence. As with other carcinomata, early diagnosis is of great importance. The textbook picture of great weight loss, chest pain, pleural effusion, copious sputum and haemoptysis represents a late phase of the disease. Among the common early symptoms are persistent cough, blood streaking, thoracic discomfort, slight weight loss, and slight anaemia. Adequate roentgenographic examination is of the greatest importance. Bronchoscopy and biopsy will confirm the diagnosis in approximately three-fourths of the patients. Aspiration biopsy probably should be reserved for neoplasms at the lung periphery and should follow attempted diagnosis by bronchoscopy. Lobectomy for carcinoma is to be condemned. Even with peripheral tumors the necessary mass ligation used in lobectomy is inadequate.

and unsurgical The rational procedure is total pneumonectomy with individual ligation of the hilar structures, high amputation of the stem bronchus and thorough dissection of the mediastinal lymph nodes Preoperative preparation should be adequate A high caloric, high vitamin diet with vitamin concentrates is given Anaemia is corrected and transfusions given when necessary Where possible, a pneumothorax is established and approximately 70 per cent of the lung is collapsed This allows for compensatory readjustments in breathing and in circulation The pleural cavity is vaccinated by 50 cc of sterile beef broth containing one per cent peptone forty-eight to seventy-two hours before surgery Intratracheal cyclopropane anaesthesia is preferable The authors prefer the anterior approach The hilar structures are ligated separately The phrenic nerve is crushed above the pericardium Novocain is injected into the pulmonary plexus of the vagus nerve, this is important in quieting the cough reflex Ligation of the artery should precede ligation of the veins, this will ensure that blood is not pumped into the lungs and lost The bronchus is treated according to the method of Rienhoff All visible lymph nodes are carefully removed If there has been no gross contamination of the pleura, the chest is closed without drainage A pneumothorax needle is introduced and the pressures are adjusted well on the negative side If the pleural cavity is grossly soiled during operation, air tight closed drainage should be instituted before the patient leaves the table Postoperatively, intranasal oxygen is always administered for several days Intrapleural aspirations of fluid and air are performed every twelve to twenty-four hours as long as fluid forms When there is evidence of infection or a leak in the bronchial stump, immediate underwater drainage is instituted If the drainage is not performed without delay in case of bronchial leak, the patient may drown in his own secretions Five illustrative cases with one operative death are reported — *Pneumectomy for Bronchiogenic Carcinoma*, P C Samson & E F Holman, *West J Surg*, May, 1940, 48 275 — (H R N)

Silicosis — The authors, with the help of a number of physicians in various parts of the country, made a survey of the silicosis problem and this paper presents the results of that survey The diagnosis of silicosis depends upon accurate interpretation of satisfactory roentgenograms, preferably stereoscopic films The elimination of the X-ray specialist in the diagnosis of this disease has, no doubt, led to unfairness to the laborer and to the industry which he serves Roentgenograms of persons who have inhaled quantities of certain mineral dusts over long periods of time show findings that are not observed in those not so exposed Those exposed to certain mineral dusts show marked changes in the forms of deposits of tissue composed mostly of collagen The amount of morbid tissue may be so slight that it is not discernible to the naked eye and even may be overlooked on microscopical examination, or it may be so great as to practically fill the thoracic cage But even slight deposits of morbid tissue are quickly discernible to the trained eye and well recorded by the standard photometer The distribution of inhaled particles in the lung is bilateral and relatively symmetrical Much of this material is laid down along anatomical structures, but nodules or spherical whorls of collagen do not conform to anatomical structures Roentgenological findings may be considered as to the characteristic pattern as seen in the roentgenogram and the regional distribution of densities on the roentgenogram Tissue deposits in pneumoconiosis fall into four main patterns and two or more of these may be seen in the same X-ray film The four patterns described are accentuated hilar and linear markings, nodules, pockmarks, and general nondescript haze or cloudiness The first considered, the accentuated hilar and linear markings, is the type described by Pancoast as the perivascular-peribronchial lymph node manifestation of pneumoconiosis The shadows are due either to dust laden phagocytes caught in a "traffic jam" on the way to the hilum, or to deposits of collagen around blood vessels and bronchi, or to a proliferation of fixed cells Subjects exposed to relatively small amounts of some mineral dusts often manifest a definite increase in the density and size of the hilar

shadows. These infiltrations or deposits may involve the nodes or extend out along the branches of the large blood vessels and bronchi. Others with the same dust exposure develop accentuated hilar markings in the middle third of the lung. The markings run parallel to medium sized bronchi and blood vessels. Likewise accentuated linear markings may occur in the peripheral third. Here the lung markings are fine and few and are due to collagen deposits along the terminal vessels and bronchi. Increased markings in this area may produce general mottling and in the past this particular type has not been differentiated from other patterns. Accentuated linear markings are a definite manifestation of pneumoconiosis, but the lesion is of little clinical significance in the early or even moderately advanced stages. The subject usually lives to old age without suspecting that he has a lesion in the lungs. This type of a lesion is a social and economic problem to both labor and industry, for a patient who is able to work and wants work may not be able to get another job because he has such a lesion. Industry, on the other hand, does not want to assume the responsibility of compensation for a man with such a lesion who is able to work but does not want to. Legislative acts do not differentiate between this type of pneumoconiosis which does not require compensation and the more serious types which deserve compensation at some stage in the disease. Nodular silicosis is the conventional type on which the diagnosis and even the definition of silicosis is based. The nodules are composed of collagen laid down like layers of onion, are bilateral, symmetrical and separated from one another by ventilated lung. Later they may grow together in round masses in the midlung field resembling a pawnbrokers sign. On X-ray they appear as white spots on a dark background. The authors' observations indicate that these nodules, considered pathognomonic of silicosis, are frequently not caused by silica. Light and dark field examinations of nodules show an overwhelming preponderance of black flecks that are not silica crystals and only a relatively few refractive crystals of silica. Therefore, it seems irrational to consider silica crystals as the aetiological factor in the

development of nodules. The lungs may be shot full of these without the patient having dyspnoea or any other symptoms and these persons may live to old age without knowing that they have nodular pneumoconiosis. Such persons are able to carry on hard labor at the prevailing wage. One, therefore, questions whether they should be prevented from getting jobs or lose the jobs they have. Legislative acts are formulated primarily around this type. "Pockmarks" are seen as numerous small areas of diminished density causing black spots about one-eighth of an inch in diameter surrounded by a white ring of increased density in the roentgenogram of individuals subjected to certain mineral dusts. This is the direct reverse of the nodule. The lesions are bilateral and relatively uniform in distribution, though more marked in the peripheral one-third. They may be more advanced on one side. The dark spots are caused by air cysts in the lung which are surrounded by lung tissue made relatively dense by collagen laid down in the form of whorls or strands. The cysts correspond anatomically to terminal lobules. As the condition progresses the pockmarks may be obscured and the mottling caused by them is increased in density by the laying down of collagen until the mass becomes a relatively solid area. These cysts are of more clinical significance than nodules and are more apt to be associated with dyspnoea, but they should not be used as the only criterion to determine whether the patient is incapacitated for work. Since these air cysts, with the pockmarking which they cause, have not been recognized before, they play no part in legislative acts. The authors believe that their occurrence in relatively dense lung may play an important part in determining when compensation should begin. Rapidly developing or acute silicosis is seen in the roentgenogram as a general haze or diffuse cloudiness which obscures normal lung markings. This haze is caused by thickening of the alveolar wall, incomplete filling or consolidation of alveoli and air passages with various types of material and envelopes of collagen surrounding the smaller blood vessels and bronchi. The perivascular and peribronchial deposits of dust-laden phagocytes, the laminae of collagen and the nodular whorls

and the areas of massive collagenization are absent or extremely scanty in this type, even in the terminal stage. The alveolar walls may be eight or ten times normal size due to deposits of collagen in certain regions and intense dilatation and engorgement of the capillary network in others. Collagen about the vessels results in marked constriction of the vessels so that there are avascular areas and hypervascular areas. This type presents a serious economic and social problem. Those afflicted deserve adequate compensation as soon as the diagnosis is established and certainly as soon as dyspnoea develops. Injustices have been done in the past because the roentgenograms did not show definite nodulation and consequently there was a tendency not to consider the lesion silicosis and therefore not within the law. As pneumoconiosis progresses, the pathological tissue is increased so that massive deposits of collagen may obliterate the pattern. This occurs in three regions of the lung. In the midlung field the deposits take the form of a pawnbroker's sign on the right, on the left one of the masses is usually missing. A large deposit of collagen may be found at the apex of the lower lobe, the upper surface of the shadow being well defined and resembling the dome of the diaphragm while the under surface is irregular and fades into the mottling of the rest of the lung. Masses of collagen with no characteristic pattern may develop in the upper lung fields and vary in size. As massive collagenization progresses the blood supply is impaired permitting inflammatory lesions to develop. Infections, pyogenic, tuberculous, or both, may be engrafted in areas of massive collagenization or in avascular areas. While displacement of the trachea and interlobar fissures does not occur, tenting of the diaphragm, obliteration of the costophrenic angle and obscuring of the left border of the heart are frequently observed when an inflammatory process is superimposed on pneumoconiosis. Cavities may be found as the result of the breaking down of tuberculous or nontuberculous inflammatory areas of collagenization. Spontaneous pneumothorax, usually occurring near the apex, and split pleura occurring high upon the lateral wall, two or three inches from the apex may also develop

When there is an increase in the linear markings or nodules present, the differential diagnosis may be somewhat difficult. The former type of pneumoconiosis must be differentiated from pneumonia, inflammation due to post-natal dripping, the chronic passive congestion of cardiac decompensation, neoplasms and bronchiectasis, while in the nodular type pulmonary tuberculosis, miliary tuberculosis, yeast infection, neoplastic metastases, actinomycosis or lobar pneumonia may have to be ruled out. Pockmarks are readily differentiated from lobular pneumonia. The diffuse haze of the acute lesion is rarely seen in other diseases. A regional approach to diagnosis is also described. With this method, films are best observed at some distance, squinting the eyes so that one does not see the pattern. The lung field is then considered in three divisions—the apex, midlung field and base. It was found that by using the photometer or "electric eye" that the amount of light passing through the negative could be accurately determined and the densities of various diseases charted and graphed. Five readings with the photometer were made on each lung. In a normal lung the graph took the form of a capital V with a proximal vertical arm. Pneumoconiotic lungs showing increased marking gave a capital W for each lung while the graph of a tuberculous lung resembled a square root sign for one lung and a W for the other. Typical readings of a neoplastic lung gave a capital V with the distal arm vertical. It is believed that with this accurate way of measuring densities and charting results an unbiased interpretation of lung densities is available which would be of value in industrial surveys for it would enable the roentgenologist to differentiate increased lung markings of pneumoconiosis from other lesions and aid in differentiating the morbid changes due to dust in different industries. The general principles and technique of chest ray films is discussed and a plea made for standard distance, good penetration and adequate, but rapid time exposure.—*The Roentgenologic Diagnosis of Pneumoconiosis (Silicosis) and Use of the "Electric Eye" to Determine Regional Densities*, L. G. Cole & W. G. Cole, *Radiology*, September, 1939, 33 261—(G. F. M.)

**Silicosis in Slate Quarriers**—A survey of 117 workers in the slate quarry industry in Blaenau Ffestunog, Merionethshire shows that silicosis of some degree was present in 62.4 per cent of those examined. The occurrence of tubercle bacilli in the sputum is high in both the entire group and the silicotic group, 15.6 per cent and 12.5 per cent, respectively. The industry contributes to this high morbidity and mortality from pulmonary tuberculosis. More careful study is warranted with a view to inclusion of this industry in the Workmen's Compensation Act.—*Silicosis in Slate Quarry Miners, T. W. Davies, Tubercle, September, 1939, 20: 543*—(A. P.)

**Prevention of Silicosis**—The cooperation of siliceous and nonsiliceous dusts in the origin and development of silicosis was investigated partly with regard to the possibility of obtaining practical methods of preventing silicosis by inhalation of harmless dusts, and partly with regard to the existence of dusts which conceivably enhance the toxicity of silica. The foremost inorganic nonsiliceous dusts tested were coal, soda, calcium hydroxide, aluminum hydroxide, metallic aluminum, iron oxides, and magnesium oxides. Siliceous dusts included quartz, colloidal and amorphous silica, lepidolite, cement and glass. These substances were tested separately and in various combinations. Most of the mixed tests were done with quartz dusts. Particle size varied but a great part of the dust was under 10 micra and to a great extent under 5 micra. Experiments were conducted by subcutaneous injection, by blowing the dust into the trachea of rabbits and by inhalation in dust chambers. The experimental animals were rabbits and guinea pigs. Chemically indifferent dusts, such as coal, had no effect on the development of silicosis, either inhibitive or promotive. Inhalation of alkaline dusts, such as soda and calcium hydroxide often caused irritations in the lungs and necrosis with inconsiderable fibrotic response. Similar changes appeared when these dusts were mixed with silica but there was no direct sign that the toxicity of the silicon was increased by the presence of alkaline dusts. These animals showed great susceptibility to pulmonary infections which, in early

stages, led to death in the silicotic animals. Positively charged metallic dusts may diminish the toxicity of the negatively charged silica. Aluminum dust, especially in pure metallic form but also as the hydroxide, considerably retarded the development of silicosis and had an inhibitive effect upon the development of fibrotic reactions. Iron and magnesium dusts also possessed a certain but slight inhibitory effect upon silica. In studying silicosis attention must be paid to the different basic dusts that commonly occur with silica in the air. These experiments suggest that greater attention should be given to the composition of inhaled dusts and to the combined effect of the separate products.—*The Prevention of Silicosis: Experimental Investigations on the Action of Certain Non-Siliceous Dusts and Silica in the Origin and Development of Silicosis, C. Naeslund, J. Indust. Hyg. & Toxicol., January, 1940, 22: 1*—(L. F. B.)

**Silicosis and Asbestosis**—The first factor in the development of silicosis is the entrance into the pulmonary lymphatics of excessive quantities of silica crystals. These particles are imprisoned in fibrous tissue which forms about them. The second and most important factor is the activity of tubercle bacilli which, most commonly, enter after the aspiration of the silica dust. The quantity of silica particles necessary to produce disease is not known. In order to enter the lymph channels and produce a lesion the particles must be less than 5 micra in size. These silica particles produce fibrous tissue which, when it is widespread and diffuse, results in mechanical impairment of pulmonary function. Furthermore, silica particles facilitate the multiplication of tubercle bacilli. When combined with glass, brick, or cement, silica particles do not produce the same effects as free silica. Only a small proportion of those exposed to silica particles develop silicosis. In 1924, of 2302 miners who had worked in the gold mines of South Africa for a period of ten years, 176 were suffering with silicosis. The great majority have escaped either because they have avoided tuberculosis or because they have not inhaled sufficient silica particles. However, it appears that many miners who have been exposed to



the dust for a long time may develop the disease a long time after they have left the dusty atmosphere, particularly when tuberculosis supervenes. In its preclinical form the disease is called latent silicosis and there is no way of diagnosing it at this stage. Silicosis, without tuberculosis, affects the general health only slightly. When tuberculosis is associated, the so-called infectious silicosis, the disease is serious and usually rapidly progressive. The diagnosis of simple silicosis is often a difficult matter and requires a long period of study with frequent roentgenograms. Careful sputum examination is necessary to rule out an associated tuberculosis. There is a question as to whether silicosis occurs among asbestos miners. Asbestos is essentially a hydrated silicate of magnesium also containing small amounts of iron and aluminum, analysis reveals it to contain 39.62 per cent of silica. In the process of extracting asbestos a tremendous amount of dust is created, most of which escapes into the atmosphere. The author is unable to state with any authority whether these asbestos particles can produce silicosis. In the regions of Thetford mines, East Broughton, Lac Noir and Vimy Ridge, there are 2162 asbestos miners but these men have never been studied from the standpoint of silicosis. In any case the author does not believe that silicosis exists in any significant degree as an independent disease. Silicosis may be physiological, as anthracosis is physiological. Silica particles may be found in the lungs shortly after birth. The normal adult, not working in a siliceous atmosphere, may have as much as 1 to 2 g. of silica in his lungs and bronchopulmonary lymph nodes. The author has been unable to discover any characteristic radiographic or clinical findings which would separate pure silicosis as a separate disease. It is the associated tuberculosis which produces all the well known clinical and X-ray findings. In the same way, one no longer speaks of silicosis among asbestos miners but rather of asbestosis. According to other observers, asbestosis is an insidious disease accompanied by dyspnoea and cough, with expectoration, not infrequently, of asbestos particles. This disease occurs in those who have worked in the industry for at least seven to eleven years.

Asbestosis does not predispose to tuberculosis. Death is usually caused by pneumonia, bronchitis, influenza, and very rarely by tuberculosis. The X-ray picture presents a coarser outline than that of silicosis. Observations in various mines have demonstrated that good ventilation combined with the use of masks will protect the miners from the injurious effect of the asbestos particles. In view of many contradictory opinions in the fields of silicosis and asbestosis, the whole subject requires further study.—*Mines D'Amiante, Silicose, amiantose, A. Sirois, Laval méd., September, 1939, 4 275*—(H. R. N.)

**Experimental Silicosis and Pneumonia**—To check the validity of the supposition that the silicotic lung may be more vulnerable to infection with the pneumococcus, as it is to tuberculosis, experiments were designed to determine the effect of silica on the growth of the pneumococcus in artificial media and in the living animal. Both particulate and colloidal silica were added to the culture medium. There was no difference in the growth of Type-III pneumococcus organisms obtained on the experimental and control media. Normal and silicotic rabbits were inoculated intracutaneously with an avirulent strain of Type-III pneumococcus. The silicotic rabbits were neither more susceptible nor more resistant to the organism than the control animals. An attempt was made to infect the animals by inhalations. All the animals remained active and apparently well and the experiment shows that silicotic rabbits differ in no respect from normal rabbits when subjected to an atmosphere filled with pneumococci. The reaction in both normal and silicotic rabbits to intrabronchial injection of avirulent bacilli was similar. The virulence of the attenuated pneumococci was not increased in the silicotic animals. The reaction in animals receiving virulent bacilli was similar in both normal and silicotic groups and, although the number of animals used was small, it is noteworthy that mortality was about 25 per cent higher in the control group. Rabbits that had survived a previous pneumococcus infection were reinfected with virulent pneumococci intrabronchially. The survival rate was higher in the

silicotic animals of this group In all the experiments, the silicotic nodules were resistant to the action of the pneumococci and retained the characteristics of such lesions in rabbits The presence of silicosis had no influence upon the well defined immune reactions to Type-III pneumococci that can be elicited in normal rabbits The small number of observations suggest that the presence of silicosis might enhance the resistance of the rabbit to Type-III pneumococcus infection—*Silicosis and Type III Pneumococcus Pneumonia, An Experimental Study*, A J Vorwald, A B Delahant & M Dworski, *J Indust Hyg & Toxicol*, February, 1940, 22 64—(L F B)

**Silico-tuberculosis**—It is thought that the problem of silicosis in industry has been fairly well eliminated and that in those states having compensation laws most cases suffering from silicosis have been brought to light, but there is still a significant number of men exposed to silica years ago who are now being seen with silicosis and superimposed tuberculosis Therefore, a report of the experience with silico-tuberculosis over a five year period in a hospital serving the industrial community of Detroit is presented In such an industrial centre there are or have been many possible silica dust hazards in the various industries and also many workers who have migrated to Detroit in recent years following exposure to silica in some other community Among 171 men admitted with a tentative diagnosis, 132 were definitely found to have silico-tuberculosis This represents 3.37 per cent of males admitted to the hospital from 1933 to 1938 The occupations of the group have been varied, but foundry workers outnumber all others, 73 belonging to this group, while 28 were miners The length of exposure is quite great and in many instances the interval since the last exposure and the time of diagnosis is quite protracted The average age at the time of diagnosis was 50.2 years, the average exposure 17.4 years, and the average interval since exposure 4.9 years The diagnosis of silico-tuberculosis is not always easy and must rest on the diagnosis of two coexisting conditions For tuberculosis the diagnosis is based on X-ray evidence, sputum analysis, cavity

formation and symptoms, for silicosis the criteria are X-ray appearance, history of exposure to silica dust and symptoms Treatment is unsatisfactory and attended by practically no success Uncomplicated silicosis has no treatment and tends to progress For tuberculosis alone, bed rest and the various forms of collapse therapy are successful in many instances, but in the presence of silicosis collapse therapy is usually contraindicated Thus bed rest is all that remains and this is not sufficient except in a few mild silicotics with little tuberculous involvement In a group of 21 considered to have a better than average outlook, collapse therapy was employed, but only 2 can be said to have done well One received pneumothorax and one received phrenic surgery In previous years other cases were tried with equally poor results The respiratory function is difficult to determine and the vital capacity gives no inkling of lung impairment in many instances This is especially true of silicotics A method of measuring the pulmonary function has recently been devised by Whitehead and reveals that these persons are bordering on serious embarrassment and would, of course, be unable to stand further inroad on their respiratory function by any collapse procedures The seriousness of the condition is further borne out by the fate of the 132 cases Seventy-seven are dead, 33 are in the hospital and 22 were discharged alive Of these 7 have been lost to sight and only a few of the other have done well Tuberculosis alone has a far better prognosis even in advanced cases An accurate diagnosis is most important, for the silicotic patient does not need bed rest and may be endangered by admission to an institution where there are open cases of tuberculosis The tuberculous individual without silicosis should have silicosis ruled out since the prompt use of collapse therapy may be of great value to him—*Silico-tuberculosis as Seen in a Large Industrial Center*, B H Douglas & E Tompkins, *Radiology*, April, 1940, 34 405—(G F M)

**Dust Particles Removed by Breathing**—An apparatus was devised using two thermal precipitators for measuring the percentage number of siliceous dust particles of different

size removed from dust-laden air by breathing. About 25 per cent of particles of size 0.2 micron and about 80 per cent of size 2 micra were removed. Between these two sizes the percentage removal was nearly proportional to the square root of the size. Above 3 micra the percentage removal gradually increased until at size 5 micra about 95 per cent of the particles were removed. It has not proved possible to explain the square root relationship found between size and percentage removal, theoretically, but the calculated displacements due to a combination of sedimentation and Brownian motion appear to be quite adequate to account for the removal of the particles. It appears likely that larger particles will tend to be deposited in the larger air passages and with decrease of size there will be a tendency for the particles to be deposited in smaller air passages. Owing to the subsequent expulsion of particles from the larger air passages by physiological mechanism, the size distribution of dust in the inhaled air may be some guide to the size distribution of the dust ultimately retained by the lungs—*The Percentage of Particles of Different Sizes Removed from Dust-laden Air by Breathing*, A. M. van Wyk & H. S. Patterson, *J. Indust. Hyg. & Toxicol.*, January, 1940, 22: 31—(L. F. B.)

**Hydatid Cyst**—Only 44 cases of echinococcus cysts of the lung or pleura have been noted in the literature of the United States and Canada. The disease is prevalent in Australia, Iceland, South America and some of the Mediterranean countries. Hydatid disease of the lung has occurred in only 5 patients known to have been born in North America. Two additional cases are reported. Both patients had emigrated from countries where the disease is prevalent. Greece and Argentina. The first patient was a thirty-year male who, in childhood, had often played with dogs on a sheep ranch in Greece. At the age of sixteen he noted the onset of cough and right chest pain. After spontaneous subsidence, these symptoms recurred at the age of twenty-one. Thoracotomy was done for a right pleural effusion. During the daily dressings, he noted that numerous whitish cysts were expelled

from the wound. The wound closed and he remained well until 1931 when symptoms reappeared and he was first seen by the authors. Previously he had also expectorated a "broken cyst." Roentgenograms disclosed a large smooth-walled, rounded mass occupying the lower outer quadrant of the right chest. A large echinococcus cyst was removed from the lung in two stages. The postoperative course was uneventful. He has remained well for seven years when last seen. The second patient was a twenty-five-year male who had worked on a sheep ranch in Argentina. His symptoms had begun in 1927 with sharp left chest pain followed by cough and thick gray sputum which later became thin, watery and foul. In July, 1928, pneumothorax was instituted for haemoptyses but had no effect and was promptly discontinued. He was first seen by the authors September, 1928. The preoperative diagnosis was interlobar empyema with bronchial fistula. At operation no pus could be found and a small pulmonary abscess was diagnosed. Nothing further was done, symptoms subsided and he was discharged. Slight expectoration continued but the increasing severity of the symptoms led finally to readmission in October, 1931. Hydatid disease was first suspected when patient stated that he had expectorated a piece of "skin." An echinococcus cyst of the left upper lobe was removed in one stage. The patient has remained well for six years when last seen. The presence of hydatid disease in domestic animals of the United States has been definitely demonstrated. However, the distribution is not general and appears to be more common in certain sections of the South. Special investigations of this problem have not been carried out in many sections of this country—*Hydatid Cysts of the Lung*, C. Haight & J. Alexander, *Arch. Int. Med.*, March, 1940, 65: 510—(H. R. N.)

**Lung Cysts**—Lung cysts may consist of air cysts or pneumatocoles and fluid cysts, the latter being true cysts which may discharge their contents and become air cysts. The lesions may consist of multiple thin-walled pneumatocoles found near the larger bronchi in hilar areas known as cystic bronchiectasis,

multiple small thick-walled cavities giving a honeycomb appearance, and fluid cysts. All of these probably arise as the result of definite anomalies in the lung structure, either congenital or acquired, as the result of infection and fibrosis. The bronchiectatic or honeycomb types may arise from arrested growth of a bronchial bud. They have a mucous membrane lining. If an infection does not occur, these patients go on without any manifestations. A wide open communication is present between them and the larger bronchi and air enters and leaves readily with each respiration. This type of pneumatocele is seldom seen in the periphery of the lung. The fluid cysts, seen as areas of increased density, frequently are centrally located near the hilum but may occur anywhere in the lung. They may show little change over long periods of time without evidence of inflammation or infection. After a time they usually discharge their contents into the bronchi. After this they may become filled with air or completely disappear. The differential diagnosis is difficult for they may be confused with new growth, a localized pleural effusion or interlobar effusion. The lung defect here is probably due to failure of a bronchial bud to undergo proper tubular development resulting in complete or partial atresia of the lumen. A subsequent resumption of growth and expansion of the distal portion may produce a cavity with secretory epithelium. Certain mechanical factors play a part in the inflation of pneumatoceles. When there is free bronchial communication, the factors determining the inflation of the sac are the ratio of the resistance of the cavity wall to the resistance of the normal alveolar structure supplied by a bronchiole of the same size. Thus if there is free passage of air, the air in the cyst should never exceed atmospheric pressure except in expiration when a check-valve action is present. Cysts remaining the same during inspiration and expiration have a check-valve action of some type and may produce displacement of the mediastinal structures on expiration. Some cysts continue to expand forming balloon cysts and obviously are due to more than simple check-valve action. Such cysts are probably due to a check-valve and an accessory air chamber producing some pump-like ac-

tion during respiration. A local pleural effusion could result in a pneumatocele and with a check-valve action produce a cyst appearing to be in the lung. Lipiodol does not enter cavities where there is no free communication and is of little value in diagnosis. Pneumatoceles arising from peripheral tissue are usually thin walled, often multiple and may be bilateral. They do not seem to be preceded by fluid cysts and have no secretory lining. In the anteroposterior view they may have the appearance of pneumothorax. Pneumatoceles of this type constitute the bulbous form of emphysema and may show no change for long periods of time, or may continue to enlarge almost completely replacing the lung structure. It is possible that they may occur as the result of congenital defects in the elastic structure of the alveolar walls.—*Cystic Disease of the Lung*, L. R. Santi, *Radiology*, August, 1939, 33 152—(G F M)

**Atherosclerosis of Pulmonary Artery and Pulmonary Emphysema**—These two conditions were at first thought to be interrelated, especially through the studies of Fischer and Munzer. Later this theory was apparently disproved by other observers who reported a small percentage, or a slight degree, of atherosclerosis of the pulmonary artery in patients having pulmonary emphysema. The striking difference of opinion between these observers may be explained by the fact that Fischer and Munzer probably limited their observations to the main trunk and larger branches only of the pulmonary artery, thus uncovering a high incidence of concurrence of the two pathological conditions, while later observers seem to have taken into consideration the smaller branches, too. A macro-microscopical study of the pulmonary artery in 10 cases of chronic essential pulmonary emphysema was made with complete examination of all large and small arteries and veins down to the capillaries. The special technique followed in this study is given in detail. Typically atherosclerotic lesions were noted in the main trunk and in the principal branches of the pulmonary artery, such lesions were absent in all branches with a diameter of 1 mm or less, where, on the contrary, a very marked

dilatation and atrophy of all vessel walls were observed, with complete absence of atherosclerotic phenomena. Capillaries were often seen enormously overdistended by the blood, unusually increased in volume and deformed. The pathogenesis of these peculiar vascular conditions is to be found in the grave hydrodynamic disturbance of the lesser circulation following the enormous reduction of the capillary bed in an emphysematous lung.—*Atherosclerosis dell'arteria polmonare ed enfisema polmonare cronico ipertrofico essenziale*, R Toselli, *Arch di pat e clin med*, December, 1939, 20 272—(S L)

**Interstitial Emphysema**—Interstitial emphysema of the lungs may follow injury or greatly increased intrapulmonary pressure and may be recognized clinically by the presence of air in the subcutaneous tissues about the neck. This particular type of emphysema is to be differentiated from the vesicular emphysema produced by bronchial obstruction and subsequent dilatation of the alveoli. Hamman in 1937 reported 6 such cases and since then no others have been found in the literature. Therefore it is felt the report of this particular case is of interest. The patient was a twenty-seven year old male who experienced sudden sharp pain in the left chest. Subsequently he felt substernal tightness and dyspnoea. Examination revealed a small pneumothorax on the left and air in the tissues between the anterior surface of the heart and the chest wall. After three weeks of rest he was entirely well. Interstitial emphysema must be differentiated from coronary artery disease and pericarditis. It is characterized by a sudden onset of sharp pain in the chest, accompanied by a choking sensation, dyspnoea and substernal tightness. Often a loud, crunching, grinding, crackling sound synchronous with the heart can be heard and in some cases air may be demonstrated in the mediastinal tissues. The treatment is symptomatic and the prognosis is usually favorable.—*Spontaneous Interstitial Emphysema of the Lungs, Report of an Additional Case*, B P Wolff, *Ann Int Med*, January, 1940, 13 1250—(A A E)

**Interstitial Emphysema**—Interstitial emphysema can be produced in cats and other animals by passing a truncated catheter into a region of the lung and blowing air into it. Thus the alveolar walls are extended with production of many small ruptures in their floors, which overlie the small branches of the pulmonary blood vessels. Correct postmortem fixation of the lungs is necessary to visualize the course of this perivascular air. The lungs are removed immediately after the experiment and filled with a fixative. The lungs are hardened in the same fixative for a day or two. In sections of such fixed tissue, the air has diffused out, but the pattern of the bubbles is well seen. Frequently, the vessels are obviously encroached upon by the pneumatic armature, and occasionally are completely collapsed. The most striking accumulations are in the roots of the lungs where the converged air streams have merged into large blebs, here the air block is of greater importance since main vessels are involved. In experimental animals the air was seen only in the sheaths of the pulmonary vessels, never in the sheaths of the bronchi or bronchial vessels. Increased pressure with further leakage of the air may produce a perforation of the mediastinum. Sometimes the air extends into the retroperitoneal tissues, down into the groin and leg, upward into the root of the neck, face, axilla, chest wall and arm, forward between the parietal pleura and pericardium, to appear as blebs overlying the heart (pneumoprecordium), and laterally into the opposite lung or unbloated parts of the same lung. Pneumomediastinum, particularly, may lead to great circulatory embarrassment and death in the animals. Rupture of the mediastinal wall sometimes produced pneumothorax. The effect of the latter is to relieve the pressure in the mediastinum and lung, thus freeing the circulation, at the same time, by collapsing the lung, it stops the leakage of air into the vascular sheaths. However, in the animals the pneumothorax was always double and complete and resulted in death. Clinical parallels for these various types of pneumogenic pneumatization of the interstitial tissues have been described. The author believes that so little is known about the problem in

## INDEX OF SUBJECTS

- A**
- Abortion and tuberculosis, 70:49-60
- Abscess(es)
- cold, spontaneous, of chest wall, 62 (Supplement, July:48-67)
  - pulmonary
    - acute, 61:474-481; 69:673-681
    - pancreatic desoxyribonuclease in, 76:1-21
    - in tularemia, (case reports) 65:627-630
- Abstracting philosophy, (editorials) 62:446-448
- (4)-Acetylaminobenzal thiosemicarbazone. *See* Thiosemicarbazones
- Achalasia, (case reports) 76:489-490
- Acid(s)
- amino
    - metabolism, detected in urine from tuberculous patients, (Notes) 76:867-870
    - relation to problem of host resistance to tuberculosis, (Notes) 66:378-380
    - of urinary excretion
      - in normal subjects on controlled diets, 60:439-447
      - in tuberculous subjects on controlled diets, 60:448-454
  - ascorbic
    - tuberculininhibitory properties and inhibition of tubercle bacilli by urine, 69:406-418
    - in tuberculosis, 64:381-393
  - fatty
    - in calf lung, effect on tubercle bacilli, 75:630-637
    - in rabbit tissue, resistance of tubercle bacilli, 69:710-723
  - heterocyclic, hydrazides and derivatives in experimental tuberculosis, 67:366-375
  - isonicotinic, hydrazide. *See* Isoniazid
  - kojie, as inhibitor of tubercle bacilli, 61: 739-741
  - para-aminosalicylic. *See* Para-aminosalicylic acid
  - phthienoic, and related acids, cellular reactions, 65: 655-672
- Acid-fast bacilli. *See* Bacilli and Tubercle bacilli
- Acidosis, respiratory, induction by oxygen breathing, 77:737-748
- Acoustic basis of chest examination, 72:12-34
- ACTH. *See* Hormones, corticotropin
- Actinomycetales. *See* Fungi
- Actinomycosis. *See* Mycoses
- Addison's disease, with histoplasmosis and pulmonary tuberculosis, (case reports) 72:675-684
- Adenitis, tuberculous
  - mediastinal and hilar, 76:799-810
  - treatment of, report by ATS Committee on Therapy, 68:392-395
- Adenoma. *See* Tumors
- Adenomatosis. *See* Tumors, adenomatosis; and carcinoma, alveolar
- Adolescents, nutrition and tuberculosis in, 74 (Supplement: August, 173-183)
- Adrenocortical function
  - and tuberculin sensitivity, 73:795-801
  - in tuberculosis, pulmonary, 64:630-644; 66:364-372
  - during isoniazid therapy for, 70:841-851
  - relationship with stress and, 69:351-369
- Adrenocorticotrophic hormone. *See* Hormones, corticotropin
- Aerosol, amphotericin B used as, (Notes) 80:441-442
- Agar diffusion
  - precipitation techniques, in determining mycobacterial antigenic relationships, 73:637-649
  - double, in tuberculosis, 77:462-472
- Aged persons
  - resection in, 73:40-51
  - tuberculin sensitivity in, 75:461-468
  - skin, 77:323-328
- Agglutination, collodion, effect of histoplasmin skin tests, 66:588-593
- Agitator, for bacteriologic specimens, (Notes) 70:176-177
- Agranulocytosis
  - due to amithiozone, (case reports) 65:339-343
  - during streptomycin treatment of miliary tuberculosis, 59:317-324
- Air. *See also* Pulmonary function
- embolus during pneumoperitoneum, (case reports) 72:537-538
  - flow, physics of, in emphysema, 80 (Supplement, July:123-125)
  - hygiene in tuberculosis, 75:420-431
  - pollution and bronchitis, (editorials) 80:582-584
  - travel in tuberculosis, 61:678-689
  - velocity index, 62:17-28
  - ways, chronic obstruction of, pulmonary diffusion in, 71: 249-259
- Air-borne infection in rabbits, 73:315-329
- Alaska, histoplasmin sensitivity of natives, (Notes) 79:542
- Alcohol, effect on tubercle bacilli in sputum, 68:419-424
- Alcoholism in the tuberculous before and during hospitalization, (editorials) 79:659-662
- Aldinamide®. *See* Pyrazinamide

lead to the same result, namely a hypoionization of the blood calcium. Any decrease in calcium ions increases neuromuscular excitability and thereby may lead to the symptoms of tetany. It is emphasized that the amount of calcium ions in the blood depends on the amount of total calcium as well as on the reaction of the blood. Any shift to the alkaline side reduces the number of ions. The most frequent cause of spontaneous hyperventilation leading to hyperpnoea is a sexual neurosis. Occasionally hyperpnoea occurs as a sequel to *encephalitis lethargica* or as a symptom of increased intracranial pressure. The neurotic fit may be interrupted by an increase of carbon dioxide tension in the respiratory air. As this method is usually not available for the practitioner, breathing through a folded cloth is recommended with the aim of producing a slight asphyxia. Intravenous calcium injections increase the total amount of calcium and thereby may replace the calcium ions lost in the allolotic stage.—*Die Atmungstetanie*, P. H. Rossier, *Schweiz med Wchschr*, April 22, 1939, 69 357—(A B T)

**Atelectasis**—The history of pulmonary atelectasis and previous classifications of types are reviewed. Attention has been focussed recently on massive collapse, on which many statistics have accumulated. This condition is much less common postoperatively now than previously, routine treatment after operations is apparently responsible for the decline in incidence. Among the procedures to prevent the development of massive collapse, carbon dioxide inhalation, intravenous injection with hypertonic solutions and postural treatment have been effective. The cause of massive collapse is still obscure. There is an increasing trend to attribute it in part to an allergic, neurogenic response leading to a bronchial angioneurotic oedema. Diagnosis is not difficult when a whole lung is involved, but is hard to establish in the case of smaller lesions involving only a portion of a lung. Pulmonary infiltrations must be distinguished from it in the differential diagnosis, and an additional difficulty lies in the fact that atelectasis is often complicated by infiltration. Two cases illustrating diagnostic problems are cited—

*Atelectasia pulmonar*, L. A. Passalacqua, *Bol Asoc med de Puerto Rico*, April, 1940, 32 130—(E R L)

**Cholesterol Granulomatosis of the Lung**—This is the report of a study of material obtained at autopsy from a man seventy-four years old who died of acute bronchopneumonia three days after the onset of the terminal illness. He had been hospitalized in the same clinic four years previously for an acute pyelonephritis and the presence of diabetes mellitus was noted at that time. The latter condition was controlled by diet alone, and during his last year of life he was eating chiefly meat and vegetables with little bread, potatoes or fruit. The findings at autopsy were not remarkable save in the lungs. There was a moderate degree of coronary and generalized arteriosclerosis. The pancreas contained much fat and the islet tissue was for the most part gone. There was no gross lipaemia. The lungs, besides evidences of bronchopneumonia in both lower lobes, contained many crystalline foreign bodies. The latter were particularly numerous in the lower lobes especially about the vessels in the main septa and occasionally in the alveolar septa. In the middle lobe of the right lung they were situated chiefly in foci of varying sizes in the pleura. They were never seen in the vessel walls or the walls of the bronchi and alveolae. Numerous chemical tests demonstrated that these crystals were cholesterol. The crystals were all contained within one or more giant cells, and there was a complete absence of true granuloma formation with lymphocytes and epithelioid cells. There were no elastic fibres in and about the giant cells, no pigment bodies, phagocytized cells, *corpora amylacea* etc. There was no deposition of calcium. Very few of the giant cells present did not contain crystals. In the lungs as a whole there was only a very slight deposition of fat. This deposition of cholesterol is postulated to have been the result of a disturbance of esterization either locally in the lung itself or hormonal from the adrenal gland. Tissue reaction to these deposits of cholesterol seems to stop with the formation of foreign body giant cells and does not lead to fibroblast formation and vascularization as occurs in Schul-

*American Trudeau Society, statements, cont.*

- present status of skeletal tuberculosis, 74:814-817
- problem of so-called "good chronic" case of pulmonary tuberculosis, 64:643-646
- recommended standards for home care of patients with tuberculosis, 78:655-656
- role of Committee on Therapy in the American Trudeau Society, 66:644-646
- treatment of tuberculous meningitis, 70:756-758
- by Committees on Therapy and on Administrative Problems, acceptable standards in the treatment of tuberculosis, 73:607-608
- by Executive Committee, the chest roentgenogram and chest roentgenographic surveys related to X-ray radiation effect and protection from radiation exposure, 77:203-208
- by Laboratory Subcommittee, hypopharyngeal (laryngeal) swabbing for the cultural diagnosis of pulmonary tuberculosis, 73:970-972
- by Subcommittee on Pulmonary Function, 73:152-155
- streptomycin-tuberculosis research project, 59:140-167
- tuberculosis hospital medical and administrative standards, 72:699-709
- tuberculosis mortality among residents of large cities (1947-1949), 66:109-116
- "Tuberculosis: A World-Wide Problem" conference, papers from (November 18, 1958), 79:684-694
- Amines, primary, simple, *in vitro* and *in vivo*, 61:407-421
- Amino acid. *See* Acids
- (4)-Amino-4' B hydroxyethylaminodiphenyl sulfone. *See* Hydroxyethyl sulfone
- Aminophylline as bronchodilator agent, 77:729-736
- Amithiozone. *See* Thiosemicarbazones
- Amphotericin B
  - as aerosol, (Notes) 80:441-442
  - serum concentrations in man, (Notes) 77:1023-1025
- Amylase, content of pleural fluid in pancreatitis and other diseases, 79:606-611
- Anaphylaxis, to viomycin, (case reports) 75:135-138
- Anemia
  - aplastic, following use of streptomycin-PAS, (case reports) 68:455-457
  - hemolytic, following treatment with PAS, (case reports) 76:862-866
  - sickle-cell, and hepatic tuberculosis, (case reports) 67:247-257
  - and tuberculosis, 65:735-743
- Anergy, in tuberculous patients
  - changes in tuberculin sensitivity when treated with antimicrobial therapy, 67:286-291
  - and prolongation of life, 67:292-298
- Aneurysm, Rasmussen's, in pulmonary tuberculosis, 60:589-603
- Angiocardiography in artificial pneumothorax, 62:353-359
- Angiography in advanced pulmonary tuberculosis, 71:810-821
- Angiopneumography and bronchography in tuberculous fibrothorax, 73:61-71
- Anomaly
  - of the lung and bronchial tree, 64:686-690
  - vascular, and lung cysts, (case reports) 71:573-583
- Anorexia, treatment with insulin, 60:25-31
- Anthracite coal miners. *See* Pneumoconioses
- Anthracosilicosis. *See* Pneumoconioses
- Antibacterial agents
  - active against tubercle bacilli in seed plants, 62:475-480
  - and isoniazid resistance, (Notes) 68:283
- Antibiotics. *See* Antimicrobials and specific names of drugs
- Antibody(ies). *See also* Hemagglutination
  - antituberculous
    - masked, 72:345-355
    - studies, 72:210-217
  - circulating, to tuberculosis, demonstration of clinical studies, 75:954-957
  - technique, 75:949-953
  - hemagglutination test, 65:194-200
    - and its hemolytic modification in tuberculosis, 65:194-200
    - slide-test modifications, against tubercle bacilli, 63:667-671
  - interference by tuberculoprotein and polysaccharide in pulmonary tuberculosis, 73:547-562
  - lung-specific, in rabbits, 78:259-267
  - protective, in tuberculosis, 76:256-262
  - tuberculous
    - by agar diffusion, 74:229-238, 239-244
    - in human serum, 74:239-244
    - in rabbit serum, 74:229-238
- Antigen(s)
  - BCG extract, from sheep erythrocytes, 75:958-964
  - fungal, sensitivity to, in students, 73:620-636
  - mycobacterial, serologic investigations of, 73:563-570, 571-575; 74:756-763, 764-772; 75:958-964
  - PPD and others, prepared from atypical acid-fast bacilli and *Nocardia asteroides*, 79:284-295



tion of fluid in the free pleural space and interlobar fissures which is probably the result of transudation due to altered capillary permeability—*Structural Changes in the Lungs of Drug Addicts*, G C Cole, *Arch Int Med*, November, 1939, 64 1039—(H R N)

**Penetrating Wounds of Thorax**—Of 171 gunshot and stab wounds seen during a ten-year period at the Akron City Hospital, 87 were penetrating wounds. Of these, 50 were caused by gunshot and 37 by stabbing. The most common symptoms were dyspnoea, chest rales, coughing and haemoptysis. Less frequently there was cyanosis, emphysema, hicough and painful respiration. There was evidence of shock in half the cases. The most common complications were haemothorax, pneumothorax and pneumohaemothorax. Empyema developed in 3 cases, pleuritis in 12, pericarditis in 3 and pneumonia in 10 cases. Partial collapse of the lung occurred in 10 cases and pneumonia in 10 cases. A conservative attitude has been followed in treatment. Surgical treatment depends on the nature of the wound and the complications present in the individual case. By waiting before evacuation of a haemothorax one gives the lung a chance to heal before opening the chest and precludes the introduction of infection. Of 49 cases of haemothorax, pneumohaemothorax or pneumothorax, thoracentesis was carried out in 15. Infection within the chest occurred in only 4 cases. Death occurred in 7 of the 37 patients with stab wounds and in 18 of the 50 with gunshot wounds—*Penetrating Gunshot and Stab Wounds of the Thorax*, C R Steinke, *J Thoracic Surg*, August, 1939, 8 658—(L F B)

**Brucellosis and Tuberculosis**—Brucellosis is widely prevalent in Europe and America. The disease is probably contracted by contact as well as ingestion. It causes clinical symptoms and occasionally pathological anatomical lesions similar to those in tuberculosis. The two diseases may coexist. Because of the clinical polymorphism of the two diseases, it is frequently necessary, in order to establish the diagnosis, to have evidence from radiography, sputum examination and tuberculin reaction

on the one hand, and blood culture, agglutination, opsonic index and brucellin reaction on the other—*Estudio sobre la difusión de la brucelosis y su semejanza clínica con ciertas formas de tuberculosis*, R García Cerviño, *Rev Mexicana de Tuberc*, April, 1940, 2 103—(L R L)

**Oil Pneumonia**—Oil aspiration pneumonia occurs more frequently among adults than is commonly recognized. Forty-seven cases are reported, 41 of which were autopsied. The ages ranged from twenty to eighty-two years. Many of these patients were elderly individuals suffering from debilitating diseases. Neurological patients, in whom dysphagia is a frequent manifestation, formed a large part of the younger age group. Liquid petrolatum was by far the most common aetiological agent. The oil was frequently taken orally in large amounts for years as an intestinal lubricant. In addition, it was used intranasally or intratracheally, the latter usually as a lubricant in cases of tracheotomy. The fats and oils of animal origin, which are important in the production of lipid pneumonia in children, play a small rôle in adults. Vegetable oils, such as iodized poppyseed oil, are chemically nonirritating; these oils can be eliminated from the lungs even in the presence of lesions due to liquid petrolatum, as illustrated in 2 cases in this series. Oil introduced into the pharynx is capable of entering the bronchial tree without exciting reflex inhibition. In addition, the oil hinders ciliary activity by mechanically slowing up or stopping the stream of mucus normally set up by the beat of the cilia. In adults who take oil orally, pathological processes which interfere with normal cough, palatal or swallowing reflexes become important predisposing factors. The condition is therefore frequently encountered in debilitated, recumbent and aged persons, in persons with dysphagia of nervous origin and in patients in whom neoplastic or other destructive processes involve the mouth and throat. Once aspirated, the disposition of the oil appears to depend mainly on gravity and inspiratory suction. In this series, the right lower lobe was involved in 34 instances, the left lower lobe in 29 instances, the right middle lobe in 25 cases, the

right upper lobe in 16 and the left upper lobe in 13. The lower portions of the individual lobes were most often affected. In only 2 instances were the upper lobes alone involved. At the onset, the lung responds to the presence of liquid petrolatum with a prompt macrophage reaction. These cells take up the oil and appear as foam cells. Extracellular oil is usually present. The liquid petrolatum can be identified by staining and chemical extraction methods. Grossly, the involved portions of lung are gray-yellow unless inflammatory changes are present. This first reaction is followed and gradually replaced by fibrous proliferation of the interstitial tissue which appears to be in large part a foreign body reaction. Oil remains entrapped within this fibrous tissue. Ultimately there remains a mass of hyalinized fibrous tissue with the entrapped oil, a true paraffinoma. Part of the oil may be carried to the regional lymph nodes. The lesions are frequently seen in the same lobe in all the different stages of development. There are no specific signs or symptoms characteristic of this disease. The disease may be entirely symptomatic. Frequently, the condition is entirely unsuspected and is recognized only at autopsy. Symptoms were present in about half the cases. These consisted of mild, moderately productive cough, occasional chest pain, intermittent fever up to 101°F lasting for several weeks to months. In 6 cases the clinical course was characterized by repeated bouts of bronchopneumonia. The physical findings are those associated with any chronic pneumonitis. In 16 cases there were no abnormalities on physical examination. No clubbing of the fingers was observed in this series. The leucocyte count and erythrocyte sedimentation rate are not affected by the oil pneumonia *per se*, although they are affected by secondary inflammatory changes. The presence in the sputum of either intracellular or extracellular oil globules is a diagnostic aid, provided liquid petrolatum can be chemically identified and provided the patient has had no oily medication for several days before the examination. The roentgenographic findings are important. In the early stages the markings in the lower lung fields are exaggerated. As the lesions progress, linear and nodular infiltrations de-

velop until finally areas of consolidation are formed. These are almost always situated at one or both pulmonary bases. They usually lie close to the cardiac shadow and extend from the hilum to the diaphragm. Serial X-ray may show no changes for years other than gradual shrinkage of these areas due to progressive fibrosis. Enlargement of hilar shadows is not as prominent in adults as it seems to be in children. When bronchopneumonia supervenes, the X-ray film presents a confusing picture of the basal oil lesions with superimposed exudative reaction. As the bronchopneumonia subsides, the basal lesions become more distinct. The roentgen picture of oil pneumonia must be differentiated from other chronic lesions such as bronchiectasis, unresolved pneumonia, pulmonary metastasis, primary lung tumor, infarct and tuberculosis. Definite differentiation by X-ray is not always possible, and often only serial pictures and the clinical course will aid in the diagnosis. Unless the pulmonary lesion produced by the oil is so extensive that the patient dies of asphyxia, as occurred in one case, it cannot of itself be considered a direct cause of death. The patient may live for an indefinite period until carried off by his primary disease or secondary infection. Diagnosis is primarily based upon the X-ray picture and on the history of oil intake, often combined with some known predisposing factor. Administration of oil even in the presence of predisposing factors does not mean that oil pneumonia will necessarily occur. Liquid petrolatum is widely used and the relative incidence of oil pneumonia is apparently small. However, its potential danger when used promiscuously in debilitated and dysphagic patients should be recognized. — *Oil Aspiration (Lipoid) Pneumonia in Adults*, D. Freeman, H. Engelberg & W. Merritt, *Arch Int Med*, July, 1940, 66:11 — (H. R. N.)

**Effects of Industrial Gases upon Lung** — It is apparently the accepted belief that men who are exposed to irritating fumes in industry develop specific conditions of the lungs as the result of this exposure. A review of the literature fails to disclose that studies, including serial X-ray films, have been made on an employee group so exposed. Therefore, for the

past five years serial chest X-ray films of a large number of men employed in the chemical industry were made to determine the effects upon the lung of exposure to low concentration of hydrochloric acid, chlorine, hydrofluoric acid, sulphur dioxide, sulphur trioxide, phosphene, phosphorus oxychloride and phosphorus trichloride gases. Upon admission to the occupations the men have been found to have various changes in the lung tissue as evidenced by fibrosis and in some cases by calcification and fibrosis indicating healed tuberculosis. In all cases the X-ray films show no visible evidence of lung changes indicating that the gases discussed have not materially affected the lung tissue. In addition to the X-ray studies, each man received a clinical examination every three months. At the same time non-compensatory illnesses were followed through an insurance plan. The incidence of pulmonary infection in the group studied was found to be no greater than occurred in other plant employees and the death rate from pneumonia and other pulmonary infection was the same as for other plant employees. It is felt that the study has not been continued long enough to reach emphatic conclusions, but there is reasonable assurance that under the present methods of operation the men studied have not experienced any serious effects as the result of the exposures to which they have been subjected.—*An X-ray Study of the Effects of Industrial Gases upon the Human Lung, E. E. Evans, Radiology, April, 1940, 34: 411*—(G. F. M.)

**Idiopathic Pneumothorax**—In the older literature spontaneous pneumothorax was regarded as due to rupture of a tuberculous process or some other destructive process of the lung into the pleural cavity. Later it was noted that often there was no demonstrable disease and the condition was regarded as idiopathic. The theory was then advanced that in such cases an emphysematous bleb or a bleb located near a pulmonary scar ruptured, and in some cases a bleb at the surface of the lung could be demonstrated. Castex and Mizzel reported twelve cases in which rupture of the bullae appeared to be the cause. In 1938 Kirshner called attention to the fact that spontaneous pneumothorax may occur in young people who

rarely show emphysema and advanced evidence in support of the theory that idiopathic pneumothorax may be due to "a congenital pleural defect or an acquired pulmonary defect with a congenital anlage." Nine cases are described by the author which invite speculation in support of Kirshner's theory and suggest that in spontaneous pneumothorax we are dealing with a primary constitutional inferiority of the pleural structure. All of the 11 patients were male under forty years of age with an average age of twenty-one. The condition was precipitated by some petty cause or no apparent cause. Complete collapse is the rule with no demonstrable adhesions, and fluid usually is absent, though one would expect that the mechanical result of perforation and sudden collapse would elicit such a response even in the absence of disease. A recurrence of the incident is not infrequent and occurred in one patient in this series; many such cases are reported in the literature, for apparently the lung does not tend to become adherent. The author regards the familial occurrence reported by others as a major argument in favor of this being a constitutional disease, although he has no familial cases in his own series. In the absence of disease one would anticipate that the lung would reexpand in four to eight weeks. The average time for reexpansion was a little over two months in this series. One patient died with hemothorax.—*The Etiology of Idiopathic Pneumothorax, H. J. Lorge, Am. J. M. Sc., May, 1940, 199: 635*—(G. F. M.)

**Spontaneous Pneumothorax**—Spontaneous pneumothorax is characterized by sudden occurrence in apparently healthy persons without accompanying pleural exudate, fever or other constitutional symptoms, and with eventual complete recovery. It usually occurs in early adult life, more frequently in men than in women. Prolonged observation makes it apparent that patients who have had spontaneous pneumothorax do not necessarily later show evidence of tuberculosis, or at least only occasionally. Three causes for spontaneous pneumothorax have previously been recognized: (1) the rupture of subpleural alveolar vesicles, (2) disruption of the visceral pleura

by the tension of visceral-parietal adhesions, (3) the rupture on the pleural surface of congenital pulmonary cysts. In addition to these causes a fourth probable cause is the rupture of the mediastinal pleura subsequent to mediastinal emphysema. Interstitial emphysema of the lung may occur without untoward physical effort. When air reaches the mediastinum and distends the mediastinal tissues the patient usually complains of substernal pain which may radiate to the back or neck. There are no constitutional symptoms. Physical examination usually discloses diminution or complete absence of the area of cardiac dullness and in many instances a peculiar and distinctive sound heard over the cardiac area during systole. Roentgenograms usually aid in establishing the diagnosis by disclosing the presence of mediastinal air, and when air is either palpable in the neck or seen there in roentgenograms, the diagnosis is at once certain. Spontaneous pneumothorax occurred in 2 of the 7 cases of spontaneous mediastinal emphysema observed. This may occur in one of two ways. Either the air may travel along the interstitial bands of connective tissue to the pleural surface and there produce a vesicle which subsequently ruptures or the air may perforate the thin mediastinal wall into the pleural cavity. Experimental and clinical evidence support the view that in such instances spontaneous pneumothorax occurs because of the rupture of the mediastinal wall in the presence of mediastinal emphysema. It is suggested, therefore, that all patients who develop spontaneous pneumothorax should be carefully examined for the presence of mediastinal emphysema.—*A Note on the Mechanism of Spontaneous Pneumothorax*, L. Hamman, *Ann Int Med*, December, 1939, 13 923—(A A E)

**Pulmonary Oedema**—The classical explanation of the mechanism of pulmonary oedema has been based upon congestion in the lesser circulation due to failure of the left ventricle. Recent researches have, however, stressed the importance of central nervous system influence in the pathogenesis of pulmonary oedema. It is possible, in every case, to produce fatal pulmonary oedema in dogs by

suboccipital injection of 40 to 50 gamma of veratrine. Similar effects can be elicited in guinea pigs and rats. The effect is not specific for veratrine, since it can be produced by the suboccipital injection of other drugs such as aconite and strophanthin. If the animal is anaesthetized by chloral hydrate or urethane, the pulmonary oedema can be diminished or prevented. The oedema occurs within four minutes after injection and the animal dies rapidly. On postmortem examination the lungs are cyanotic and tense. Histologically, all the vessels are filled with blood. Many capillaries are dilated and packed with blood cells. Most of the alveoli are dilated, some contain exudate and the remainder air. In many areas blood is seen lying free in the interstitial tissues. The changes are focal in character. In the guinea pig and rat the oedema is mainly present at the periphery of the lung. The heart shows no dilatation. In order to study the mechanism of the reaction the authors studied several dogs who had been subjected to a suboccipital injection of veratrine. The basis of the reaction appears to be a marked stimulation of the sympathetic system. There is severe peripheral vasoconstriction. In this manner blood is forced from the greater into the lesser circulation. This overfilling of the lesser circulation together with the loss of tonus of the smaller pulmonary vessels, effected by the stimulation of the pulmonary sympathetic, accounts for the massive oedema in these animals.—*Zentrogenes Lungödem*, A. Jarisch, H. Richter & H. Thoma, *Klin Wchnschr*, November 11, 1939, 18 1440—(H R N)

**Pneumococcic Empyema**—The authors report a case of pneumococcic empyema and nodular tuberculosis complicating a Jacobaeus operation and treated by sulfapyridine orally and intrapleurally. Later, a tuberculous bacillaemia occurred as verified by four positive inoculations of the patient's blood in guinea pigs. In lavaging the infected pleural space serum containing a small amount of Lugol's solution was used, later followed by an injection of 2 cc of a 33 per cent solution of sodium Dagenan diluted in physiological serum. After six days of this treatment the pleural fluid was found

bacteriologically sterile but the patient succumbed to the bacillæmia. The pneumococcal seeding of the pleura probably resulted from a pulmonary perforation although this was not demonstrated clinically either by manometric pressure readings or by dye.—*Section de brides. Pleurésie purulente pneumococcique traitée par les sulfamide. Granulie pulmonaire avec bacillémie, D Doady, J Brailon & G Georges, Arch natl chir de l'app respir, 1939, 14 no 1, 16—(J L I)*

#### Congenital Absence of Hemidiaphragm—

A case is reported of such an abnormality in an eight year old boy, who for the last two years had complained of frequent belching and of occasional emesis following the evening meal, this latter symptom was relieved if the supine position was taken soon after the meal. A diagnosis of left pleural effusion had been made seven years previous, because of a low-grade fever and dry cough. Physical examination was negative except for a few findings in the left hemithorax: lack of expansion, tympany over the upper half and flatness over the lower half, and generally feeble breath sounds especially at the base. The spleen could not be palpated. The heart was markedly shifted to the right and the apex beat was heard back of the sternum. Radiograms, taken before and after a barium meal, showed large intestinal loops occupying most of the left hemithorax. Following the report of physical findings, there is a brief discussion of embryological and foetal development of the diaphragm. After a review of the literature and of differential diagnoses, the author concludes that the most probable hypothesis in the case presented is that of a congenital absence of the left hemidiaphragm.—*Assenza congenita dell'emidiaframma sinistro, V Fanano, Riv di pat e clin d tuberc, August, 1939, 13 576—(S L)*

**Histaminase in Hay Fever**—Histaminase has become a popular drug for clinical experimentation in allergic diseases and allied disorders. This is based entirely on the assumption that the allergic reaction is caused by the liberation of "H-substance" at the site of contact of antibody with antigen and on the

probability that histaminase might inactivate the "H substance", which is similar but not identical to histamine. Fifteen patients known to have typical symptoms of hay fever beginning about the middle of August and lasting until the first frost were chosen for study. Each patient gave a typical reaction to a 1:100 dilution of ragweed extract. On August twenty-third the high pollen concentration produced typical symptoms of hay fever in all 15 patients. The patients were instructed to take 15 units of histaminase daily, but later the dose for 6 of the patients was increased to 60 and 75 units a day. Improvement in all cases after two days coincided with a drop in pollen counts, but symptoms reappeared and became worse with rising pollen counts. All patients continued to have hay fever during the course of study. Titrated intracutaneous tests with histamine acid phosphate were made before and after histaminase therapy. This therapy did not alter the histamine reaction of any of the fifteen patients. The author concludes that histaminase is of no practical usefulness in the treatment of hay fever.—*Histaminase in the Treatment of Hay Fever, F I Keeney, J A M A, June 22, 1940, 114 2448—(G L I)*

**Potassium in Hay Fever**—In a study of the effect of prolonged administration of potassium salts, 153 patients with hay fever or hay fever with asthma received potassium chloride or potassium gluconate for periods varying from several days to a few weeks. The usual dose for adults was 10 to 15 grains of potassium chloride or from 15 to 30 grains of potassium gluconate three or four times daily. The dose for children was from 5 to 10 grains of potassium chloride three to four times daily. Of the 153 patients only 7 patients experienced mild relief, while 116 patients obtained no relief. Two patients became worse. On a group comparative basis, of 30 patients with hay fever symptoms who had inadequate or no specific desensitization therapy, 2 had mild relief and one was made worse, of 52 patients with hay fever and asthma who had inadequate or no specific desensitization therapy, only 2 obtained mild relief, of 24 with hay fever who had adequate specific therapy, but had remaining

symptoms, none were improved, of 44 patients with hay fever and asthma who had adequate desensitization but remaining symptoms, mild improvement was noted in 3 cases. The authors conclude that potassium salts have no practical usefulness in the treatment of hay fever—*Potassium Salts in the Treatment of Pollinosis: A Clinical Evaluation*, S S Rubin, A L Aaronson, M A Kaplan & S M Fernberg, J A M A, June 15, 1940, 114 2359—(G L L)

**Potassium in Hay Fever**—The authors have repeated the work of Bloom, in attempting to determine the value of potassium salts orally in the treatment of hay fever. Forty patients were treated in two groups, 9 patients in January, when there was no pollen in the air, and 31 patients in the period from June to November. Control solutions were prepared and used alternately with the solution of potassium salts. None of the first group of 9 obtained any relief. A stronger solution of potassium chloride was used with two control solutions for 31 patients in the second group. Only 2 of the group reported relief, but the control solutions also provided relief in these 2 patients. Several of the patients had no relief for urticaria and migraine, and several with bronchial asthma had no aggravation of symptoms on taking the salt. None of the patients treated with potassium had previously shown any relief from specific treatment based on cutaneous testing. The authors were therefore unable to substantiate the good results reported by Bloom in the treatment of 29 cases, in which potassium afforded degrees of relief varying from 50 to 100 per cent in all cases—*Potassium Salts in Hay Fever*, H Miller & G Piness, J A M A, April 27, 1940, 114 1627—(G L L)

**Hodgkin's Disease**—The author analyzes 212 proved cases of Hodgkin's disease, showing a preponderance in males between the ages of twenty and forty. Its occurrence is unusual in girls under fifteen. There were no apparent predisposing factors. In 79 per cent of the series lymph node enlargement was the first abnormality noticed. Unilateral lymphadenopathy was more usual in early cases.

Discharging sinuses occurred in 7 cases, possibly indicative of a concomitant tuberculosis. There was infrequency of splenomegaly in early cases. There was no uniform pathognomonic roentgenographic mediastinal picture. In no instance was there enlargement of the mediastinal nodes without palpable cervical, supraclavicular or axillary adenopathy. In 19 instances the parenchyma of the lung was dotted with nodules, varying in size from a ten cent piece to a half dollar. Fourteen individuals (66 per cent) showed roentgenographic evidence of disturbances of the osseous system. There were 10 instances of diplegia. The transverse myelitis may be explained by an epidural invasion with a resulting choking off of the blood supply to the spinal cord. The most constant blood picture was a diminution in the lymphocytes with an increase in monocytes. A continuous low grade type of pyrexia was present in most cases. The Pel-Ebstein variety was uncommon. The average duration of life after onset of symptoms of the 123 patients who died under observation was 32.06 months. The average duration of life after the institution of therapy was 23.8 months—*An Analysis of 212 Cases*, L B Goldman, J A M A, April 27, 1940, 114 1611—(G L L)

**Erythema Nodosum in Coccidioidomycosis**—A study was made of 453 patients with erythema nodosum or multiforme in Kern and Tulare counties in the San Joaquin Valley in California. A tuberculous aetiology was established or considered probable in 11 patients. Coccidioidomycosis (San Joaquin fever) was considered the cause in 432 patients. In practically every instance diagnosis was confirmed by a positive coccidioidin test. Cover slip examination, culture and guinea pig inoculation of the sputum were made in patients who had expectoration. *Coccidioides immitis* was demonstrated in 72 per cent of patients with satisfactory specimens. Physicians rarely failed to diagnose erythema nodosum, but erythema multiforme twice resulted in a diagnosis of eczema, and six times in a diagnosis of smallpox. On the other hand, patients were diagnosed as having San Joaquin fever when they were suffering with acute

appendicitis, lead colic, smallpox, secondary syphilis and tuberculosis. It was possible to determine the incubation period of the disease in several patients who acquired the infection on a brief visit to the valley. The incubation periods ranged between one and three weeks, most frequently falling around two weeks. In several instances the relationship of the erythema nodosum to development of allergy was shown by a change of reaction to coccidioidin from negative to positive at the time of appearance of the erythema. That sensitivity to coccidioidin can persist for a long time without exogenous reinfection was shown by a test made on a physician who had become infected in a laboratory in 1929. Although there had been no possible exposure to the fungus after 1932, a test made in 1938 showed a severe reaction with necrosis. Only two possible instances of recurrence of San Joaquin fever were encountered, indicating that postprimary erythema nodosum is as infrequent in coccidioidomycosis as in tuberculosis. Evidence that coccidioides spherules did not pass from man to man was shown by study of bed-mates. The endospore-forming spherules which occur within the animal host and in the sputum are apparently rarely, if ever, infectious. Infection occurs through inhalation of the chlamydo-spores characteristic of the fungus in nature and readily adapted to widespread dissemination. The seasonal distribution of the erythema attacks bears this out. The highest incidence occurred during the summer and autumn when agricultural activity is at its peak. Few cases occurred during the rainy seasons. A predilection for females was noted comparable to that of tuberculous erythema nodosum. Coccidioidomycosis appeared most commonly among presumably nonimmune young persons and recent residents. Nearly half the patients had lived in the valley less than a year. Gifford's studies with the coccidioidin test are cited. The percentage of reactors ranged from 17 per cent in school children resident in the valley less than one year to 77 per cent in children resident ten years or more. In the series of 432 patients with erythema, none developed coccidioidal granuloma, this severe and often fatal form of the disease is, however, less infrequent among Negroes

and Filipinos—*Epidemiology of Acute Coccidioidomycosis with Erythema Nodosum* ("San Joaquin" or "Valley Fever"), C. E. Smith, *Am J Pub Health*, June, 1940, 30: 600—(H L I)

**Erythema Nodosum in Coccidioides**—Seven cases of erythema nodosum, definitely proven to be associated with the *Oidium coccidioides* in children ranging from the ages of three and one-half to thirteen years, have been presented as being independent of either tuberculous or rheumatic infection. Only those specimens in which the fungus could be cultured on Sabouraud's medium, recovered from guinea pigs after inoculation and then recultured, have been classed as positive. In all instances a definite pulmonary complication accompanied the erythema nodosum, as shown by clinical and X-ray findings, but which resolved entirely within a month's time and failed to progress later into granulomatous or caseous lesions. No tubercle bacilli were ever isolated from any of the specimens, and, in all but one case, the Mantoux tests were negative—*Erythema Nodosum in Childhood Associated with Infection by the Oidium Coccidioides*, Juliet Thorner, *Arch Pediat*, October, 1939, 56: 628 (From Author's Summary)—(M B)

**Thrombosis of Superior Vena Cava**—This is a rare pathological condition although easily recognized, there having been collected from the literature only 309 cases of obstruction reported up to 1933, by Ehrlich, Ballou and Graham. Aortic aneurysms and malignant mediastinal tumors were found to account for a large percentage of total obstructions. If the cases due to thrombosis are separated the number is reduced to 120 reported in the literature up to 1936, not all these being proved, of which 29 per cent were due to external pressure, 23 per cent associated with mediastinitis and 36 per cent with phlebitis. There is an interesting group of cases with unknown etiology. A case is reported in a policeman of thirty-eight who complained of a bursting sensation in the ears, aggravated by bending down, who had had lobar pneumonia three years before and a small localized thrombosis of the right leg in 1936. His symptoms had begun

a month before hospital admission (to St Thomas' Hospital, London) and two weeks later there had been a small haemoptysis and some dyspnoea on exertion. Sputum had failed to show tubercle bacilli on concentration and chest X-rays had revealed merely a slight evidence of the mediastinal shadow, lung fields being normal with no evidence of tumor. Right artificial pneumothorax was induced with a view to thoracoscopy but the apical and mediastinal surfaces were adherent. Exploratory thoracotomy showed the superior vena cava as a hard band running from the root of the neck into the right auricle and no constricting bands or tumor were found. Signs of obstruction were somewhat less evident four

months later. It was thought that the lobar pneumonia might have been a factor by setting up a mediastinitis. The ultimate prognosis is generally regarded as unfavorable, improved circulation being possible only by canalization of the clot, but in this case the immediate prognosis seemed good. Treatment of the condition is discussed, especially radical removal of tumors and constricting bands, and palliative treatment of some cases by mediastinal decompression which is justifiable where pressure increases sufficiently to cause collapse of softer structures. Exploratory thoracotomy is advised in cases of doubtful aetiology.—*Thrombosis of the Superior Vena Cava*, E M Buzzard, *Tubercle*, January, 1940, 34: 39—(A P)

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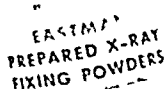
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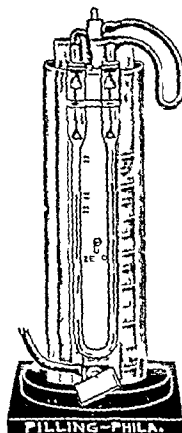
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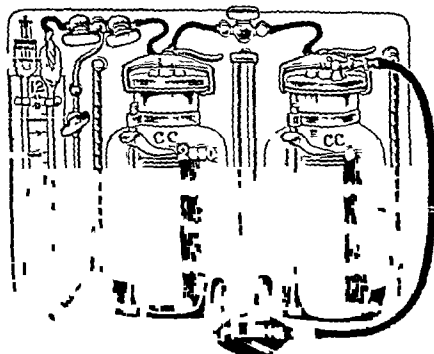
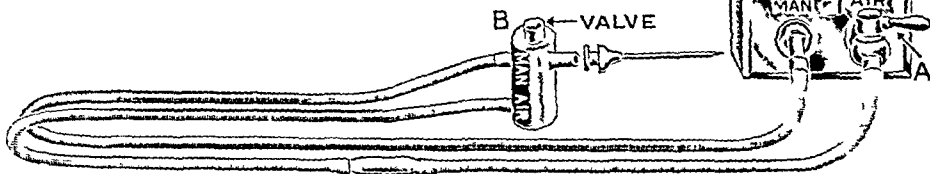
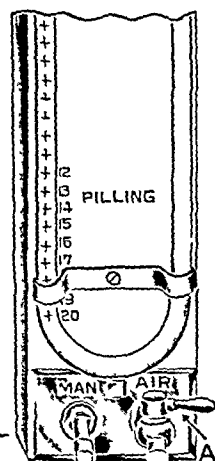
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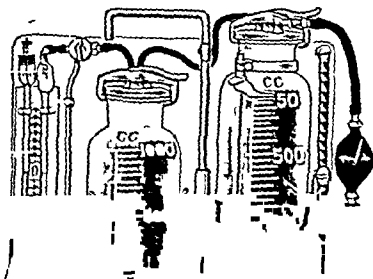
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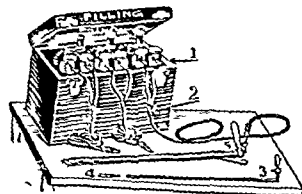
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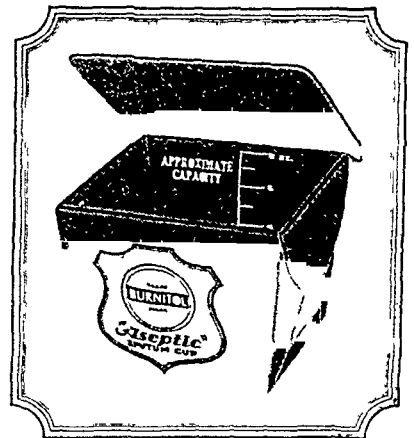
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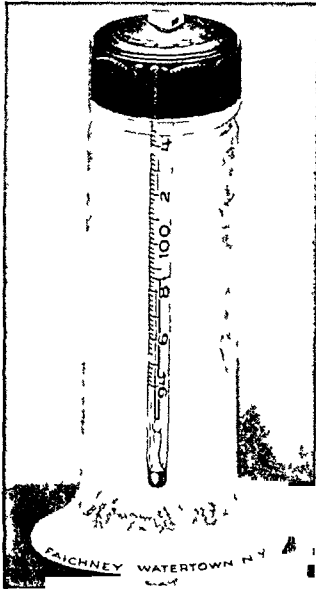
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# CONTENTS

ZACKS, DAVID	Pulmonary Tuberculosis in the Second Decade of Life I Its Development and Fatality	683
ZACKS, DAVID	Pulmonary Tuberculosis in the Second Decade of Life II Its Treatment and Prognosis	703
ROOT, HOWARD F, AND BLOOR, WALTER R	Diabetes and Pulmonary Tuberculosis With Special Reference to the Lipid Content of Diabetic Lungs	714
BRYANT, JAMES CLUTE	Oral Tuberculosis	738
WILSON, GEORGE C	Bilateral Tuberculous Pleurisy with Effusion An Analysis of Fourteen Cases	745
DE CECIO, THOMAS, AND ELWOOD, BENJAMIN J	Erythrocyte Sedimentation Its Practical Value in the Management of Pulmonary Tuberculosis	748
PARETZKY, M	The Epidemiological Aspects of the Negative Tuberculin Reaction	754
KNIES, PHILLIP I	The Detection of Tuberculosis in Group Surveys	766
DAVIES, ROBERTS, AND SCHERER, C A	Tuberculosis Survey of an Entire Community	778
SMITHBURN, KENNETH C, AND LAVIN, GEORGE I	The Effects of Ultraviolet Radiation on Tubercle Bacilli	782
HEISE, FRED H, AND STEENAEN, WILLIAM, JR	Vitamin C and Immunity in Tuberculosis of Guinea Pigs	794
WELLS, C W	Pathological Changes in Pulmonary Tuberculosis in Jamaican Negroes	796
CASE REPORTS		
BRADSHAW, HOWARD H, AND CHODOFF, RICHARD J	Anthraco-silicosis Simulating Pulmonary Carcinoma	817
FOX, THEODORE T, BURMAN, MICHAEL S, AND SINBERG, SAMUEL	An Unusual Case of Tuberculosis of the Spine	825
Index of Abstracts of Tuberculosis		91
Index of Subjects and Authors		831
Title Page of Abstracts		
Title Page of Volume		
Table of Contents		

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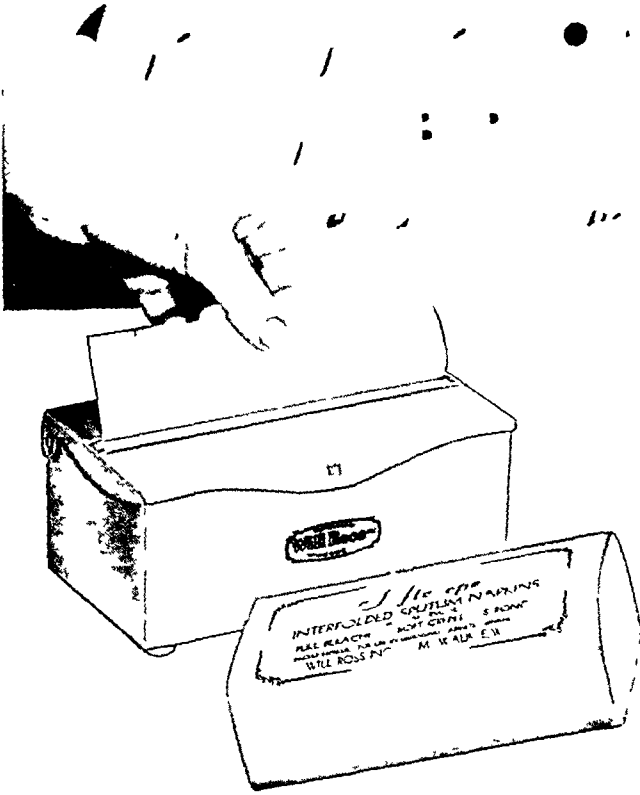
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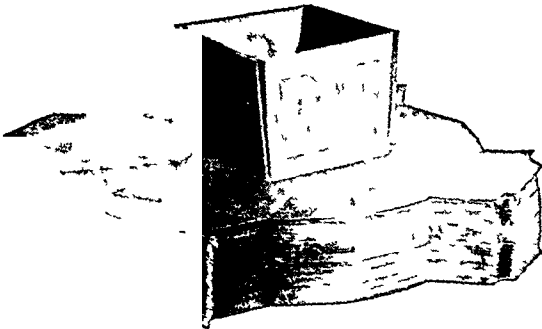
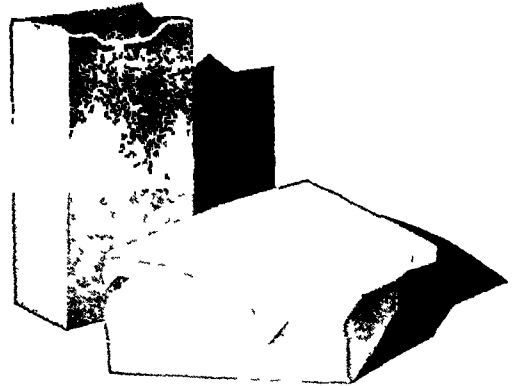
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# PULMONARY TUBERCULOSIS IN THE SECOND DECADE OF LIFE<sup>1</sup>

## I Its Development and Fatality

DAVID ZACKS

A certain proportion\* of children who survive an initial tuberculous infection in their first decade of life begin to develop subsequent disseminations or reinfections during their second decade of life. These disseminations or reinfections usually begin as minimal lesions and are encountered clinically in two phases, the symptomatic and the asymptomatic. If we wait for the patient to come to the office the great majority will present symptoms. In case-finding surveys, with routine X-ray films of tuberculin-positive children, we found that in the first stages of development pulmonary tuberculosis rarely has an acute onset. The disease in its chronic form always has an insidious, symptomless beginning, the only objective evidence being a chance X-ray finding which may, however, reveal fairly extensive lesions. In the great majority of instances the lesions are apical and vary in extent in their relation to the anterior or posterior ribs. In its acute form, pneumonic phthisis which occurred in 2 of 536 cases, the diagnosis at first was non-specific pneumonia. Those who have had an opportunity to observe these asymptomatic lesions by serial X-ray films have been indelibly impressed by their tendency to spread without symptoms, without signs, until sooner or later a considerable lung area is involved.

During the course of development and spread, no gross retardation in growth occurs in growing children. In only 4 per cent of the instances was the weight observed to become stationary with the appearance of the lesion. A cavity may develop without any objective or subjective symptoms. If a child is in a sanatorium where the temperature is observed periodically, cavity formation may be found to be accompanied by slight or moderate fever. If put to bed the patient will gain weight rapidly, the pseudo-recovery of Laennec, while the X-ray shows persistent exten-

<sup>1</sup> From the Massachusetts Department of Public Health, Boston, Massachusetts.

\* The exact proportion is being determined for a large group of children and will be reported later.

sion of the lesion in the majority of cases. An extensive haematogenous spread may occur without any symptoms. A bronchogenic spread, the result of a spill from a cavity, is usually accompanied by fever, symptoms and signs. A haemorrhagic spread will give signs, symptoms and toxaemia. There comes a time, however, when symptoms make their appearance in the slowly spreading lesions. The average interval of time for this to happen is three years, the younger the age at diagnosis the slower the spread and the longer the period of time. Toxic symptoms may not appear until shortly before death.

This clinical study is based on 536 white children who were observed carefully for a period of 2,144 person years<sup>3</sup> or an average of four person years. The longest period of observation was twelve years, the shortest period was one year.

The material came from two sources. The larger group, 443 children (137 boys and 306 girls) were discovered in the public schools. Of these, 297 were found in the schools as a result of the routine X-raying of Pirquet positive children, and 146 developed pulmonary tuberculosis during the course of observation of a large group of school children who were followed annually with check-up X-ray examinations. A smaller group consisting of 93 patients were originally tested at the school clinics but were not followed routinely. These, however, were subsequently reported as pulmonary tuberculosis, either by county clinics or private physicians, and were included in this study after the diagnosis was confirmed.

#### DESCRIPTION OF THE GROUP AT THE BEGINNING OF THE STUDY

In the 536 children were 367 girls and 169 boys, approximately two girls to each boy, 63.6 per cent had familial contact. The cumulative tuberculosis mortality in these contact families was 38.8 per cent, the case fatality 44.3 per cent (41 per cent males and 45.5 per cent females). Nineteen were in the age group five to nine years, 208 in the age group ten to fourteen years, 285 in the age group fifteen to nineteen years, and 24 in the age group twenty years and over. It is noteworthy that of the 93 reported cases 83.9 per cent were in the older age group fifteen years or more, whereas, in the school group, 52.1 per cent were in this age group, 35.5 per cent of the entire group had symptoms and/or signs referable to the chest and 12.9 per cent had positive sputum.

<sup>3</sup> A person year represents the experience of one person or patient who was observed for one year.

(boys 10.7 per cent and girls 13.9 per cent), 13.9 per cent of the entire group had cavities (boys 1.2 per cent and girls 14.8 per cent)

The school clinic group, 443 children, were all in school and presumably well. In this group the diagnosis was made exclusively on X-ray evidence in 72.5 per cent, and in only 27.5 per cent was the X-ray diagnosis supported by symptoms and/or signs referable to the chest at the time of the examination and could properly be classified as so-called "manifest disease." In the school group, sputum was positive in 6.8 per cent (3.6 per cent boys and 8.3 per cent girls)

In the reported group of 93 children, 73.1 per cent already had symptoms and/or signs referable to the chest at the time of diagnosis, as well as more extensive lesions on X-ray. In this group positive sputum was found in 41.9 per cent (40.6 per cent boys and 42.6 per cent girls)

The X-ray classification of the whole group by topography of lesions is given in table 1. The classification is based on 531 children, as the location and extent of the original lesion was unknown in 5 children.

As the shadow cast on the roentgenogram is the main reliance in diagnosis for tuberculin-positive but otherwise presumably healthy school children, the classification of these shadows according to their extent and location was found to be extremely helpful and practical. A qualitative description of these lesions, such as exudative, productive, caseous-pneumonic, is not possible with any degree of accuracy from the first film alone. The terms "progressive" and "retrogressive" are more significant in describing the course of these lesions.

Apical lesions, soft in appearance, are either homogeneous or mottled, with a fine or coarse stippling, or hard, strand-like or stringy, and may or may not be accompanied (or preceded) by calcified nodes in the parenchyma or tracheobronchial region. Such apical lesions are almost always aetiologically tuberculous. The differential diagnosis is an occasional upper lobe atelectasis, bronchiectasis or lung abscess, very rarely, congenital cystic disease, if this is confined to one or both upper lobes.

Sub- or infraclavicular shadows must be distinguished from an acute or subacute nonspecific pneumonia, which is not infrequently found in children who are able to attend school. In appearance, the transient shadow is not dissimilar to its chronic counterpart. There is almost always, however, a history of an acute "cold" or "grippe," not severe enough to confine the patient to bed. A second film which should always be made within ten days or two weeks will show either a complete

TABLE 1  
*Topography of original X-ray lesions of 167 boys and 364 girls by age groups*

AGE GROUP	6 TO 9 YEARS				10 TO 14 YEARS				15 + YEARS				6 TO 15 YEARS				TOTAL LESIONS	
	M	Per cent	F	Per cent	M	Per cent	F	Per cent	M	Per cent	F	Per cent	M	Per cent	F	Per cent	Num-ber	Per cent
Sex																		
Subclavicular	0	0	1	9	5	8	21	15	11	12	30	14	16	10	52	14	68	13
Unilateral																		
Apex above clavicle	3	38	5	46	16	25	36	25	21	22	43	21	40	24	84	23	124	23
To second anterior rib	1	12	2	18	13	20	25	17	15	16	33	16	29	17	60	17	89	17
Beyond second anterior rib	1	13	1	9	8	13	16	11	5	5	17	8	14	9	34	9	48	9
Unilateral with cavity	0	0	0	0	2	3	4	3	5	5	18	8	7	4	22	6	29	5
Total	5	63	8	73	39	61	81	56	46	48	111	53	90	54	200	55	290	54
Bilateral																		
Apices above clavicles	3	37	2	18	10	16	15	10	16	17	18	9	29	17	35	10	64	12
To second anterior ribs	0	0	0	0	8	12	12	8	4	4	10	5	12	7	22	6	34	6
Beyond second anterior ribs	0	0	0	0	1	1	10	7	6	6	13	6	7	4	23	6	30	6
Bilateral with cavity	0	0	0	0	1	2	5	4	12	13	27	13	13	8	32	9	45	9
Total	3	37	2	18	20	31	42	29	38	40	68	33	61	36	112	31	173	33
All lesions	8	100	11	100	64	100	144	100	95	100	209	100	167*	100	364*	100	531*	100

\* Five children, 2 boys and 3 girls, not included because location and extent of original lesion unknown

disappearance of the "fleeting shadows" or considerable clearing. The specific chronic shadow will persist. These lesions must also be differentiated from interlobar pleural effusion which upon clearing leaves a thickened interlobar fissure. Atelectasis, due to bronchial obstruction by foreign body, or large tracheobronchial node and pulmonary abscess must also be kept in mind.

Unilateral basal shadows are usually, and bilateral shadows almost always nontuberculous. The diagnosis in the great majority of instances is bronchiectasis or atelectasis, or a combination of both. There is usually a story of long standing cough with loose expectoration which is persistently negative for tubercle bacilli. Râles are easily elicited in either one or both bases. Basal bronchiectasis is not infrequently found in school children. Basal tuberculosis is rare.

Table 1 shows that 12.8 per cent of all the lesions were sub- or infra-clavicular, either uni- or bilateral, and 87.2 per cent were apical, 54.6 per cent of the apical lesions were unilateral, 5.5 per cent with cavities. The majority of the unilateral apical lesions were of minimal extent, that is, either above the clavicle within the first anterior rib, or from the apex down to the second anterior rib. Bilateral apical lesions were present in 32.6 per cent of the cases, 8.5 per cent with cavities. It should be noted that the older the age group the more advanced were the lesions on the original diagnosis, particularly in the bilateral lesions. For instance, bilateral lesions extending below the second anterior ribs and lesions with cavities occurred in 10 per cent (2 of 20) of the boys in the age group ten to fourteen years, against 47.4 per cent (18 of 38) in the age group fifteen or more years. For girls in the age group ten to fourteen years, the incidence of advanced lesions was 47.4 per cent (15 of 42) contrasted with 58.8 per cent (40 of 68) in the age group fifteen or more years (see table 1).

#### COURSE OF PULMONARY LESIONS

As these soft lesions were observed with serial films over a period of time, the majority showed progression, some definitely retrogressed, and some remained stationary. If such a lesion is observed early in the development (case 10, plate 4) it may be seen to spread at first and involve a certain area, then it may show retrogressive changes. On the other hand, a shadow which is definitely retrogressive at first, even to the point of partial calcification, may reactivate and progress to a fatal termination (case 11, plate 4). Stationary shadows, homogeneous or



mottled in character, may remain stationary for a longer or shorter time, then begin to spread or retrogress. Soft stationary shadows are always uncertain as to outcome until definite changes occur which will indicate their behavior. Strand-like or stringy shadows, either apical or subclavicular, tend to remain stationary for a long time with rare exceptions and, after puberty has passed, may remain stable.

Lesions of minimal extent that progress do so on the whole rather slowly and silently. If apical, the spread is downward as if by contiguity, first on the affected side, then on the contralateral side if this is not already involved. If bilateral, both sides may spread simultaneously. When a cavity spills over, the consequent bronchogenic dissemination may be rapid indeed. Occasionally, a small lesion either apical or subclavicular has a sudden rapid spread to both lung fields which can be explained only by haematogenous or lymphatic dissemination. When this appears, both lung fields are spotted with innumerable shadows of fine or coarse stippling. Subclavicular lesions on the whole tend to spread more rapidly and develop cavities more often and more quickly than apical lesions of similar minimal extent. The spread in subclavicular lesions is usually downward, but it may go in either direction.

The proportion of X-ray spread of apical lesions by age groups is not significantly different, but the period of observation is longer for the younger age groups because the younger the child at diagnosis, the slower the rate of spread. The average years of observation for the age group five to nine years was seven years, for the age group ten to fourteen years, five years, and for the age group fifteen or more years, three years.

The first thing to note in table 2 is the direct relationship of the extent of the apical lesions to mortality, the more advanced lesions give the greatest mortality during a shorter period of observation. After an average of four years, all X-ray lesions showed a spread in 63.1 per cent, 24.3 per cent retrogressed, and 7 per cent remained stationary, 5 per cent of the lesions that spread according to X-ray observation first showed a tendency to retrogress, but finally spread (case 11, plate 4). Nine per cent of the lesions that eventually retrogressed were also observed during their initial spreading phase (case 10, plate 4).

Of the children showing progressive lesions by serial X-ray films, 35.2 per cent have died within the period of observation (23.8 per cent of the boys and 40.7 per cent of the girls). The excess mortality for the

TABLE 2

*Progress of tuberculosis lesions by topography of lesions at diagnosis*

LOCATION AND EXTENT OF LESIONS BY X RAY AT DIAGNOSIS	NUMBER		MEAN YEARS OF OBSERVATION		PER CENT DEAD OF TOTAL		RESULT ON X RAY AT THE END OF FOLLOW UP PERIOD									
							Per cent progressive		Per cent dead of progressive		Per cent retrogressive		Per cent stationary		Per cent unknown	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Subclavicular lesions	16	52	3 4	3 8	6 3	17 3	87 5	63 4	7 1	27 2	6 2	30 8	6 2	1 9	0	3 8
Unilateral																
Apex above clavicle	40	84	4 5	4 1	5 0	10 7	50 0	50 0	10 0	21 4	30 0	29 7	12 5	13 1	7 5	7 1
Apex to second anterior rib	29	60	4 6	4 8	13 8	16 7	58 6	45 0	23 5	37 0	34 5	46 6	3 4	5 0	3 4	3 3
Apex beyond second anterior rib	14	34	3 9	4 5	14 3	38 2	92 8	73 5	15 3	52 0	7 1	23 5	0	0	0	2 9
Unilateral with cavity	7	22	3 8	2 8	28 6	22 7	85 7	77 2	33 3	29 4	14 2	9 1	0	13 6	0	0
Bilateral																
Apices above clavicles	29	35	4 4	4 6	6 9	11 4	44 8	48 5	15 3	23 5	27 6	22 8	10 3	14 3	17 2	14 3
Apices to second anterior ribs	12	22	4 8	4 5	33 3	31 8	66 7	68 1	50 0	46 6	16 6	13 6	0	18 2	16 6	0
Apices to beyond second anterior ribs	7	23	2 9	3 3	57 1	69 6	100 0	86 9	57 1	80 0	0	8 7	0	0	0	4 3
Bilateral with cavity	13	32	1 7	2 5	38 5	59 4	84 6	93 7	45 5	63 3	7 7	3 1	0	0	7 7	3 1
All lesions	167	364	4 0	4 0	15 6	25 3	65 2	62 0	23 8	40 7	21 6	25 6	6 0	7 4	7 2	4 9
All lesions combined	531*		4 0		22 2		63 1		35 2		24 3		7 0		5 6	

\* Five (5) children, 2 boys and 3 girls, not included because original lesion unknown

girls is due partly to the fact that they had more extensive lesions at the time of the original diagnosis (table 1), had a greater proportion of cavities and developed cavities and positive sputum more frequently. The girls developed cavities at a rate of 4.9 per cent a year, the boys, 3.7 per cent a year. The rate of the development of cavities by the topography of the lesions was as follows:

Subclavicular boys, 7.4 per cent a year, girls 6 per cent a year

One apex above clavicle boys, 1.1 per cent a year, girls 4.0 per cent a year

Both apices above clavicle boys, 2.4 per cent a year, girls 4.3 per cent a year

One apex to second anterior rib boys, 3.0 per cent a year, girls 2.1 per cent a year

Both apices to second anterior ribs boys, 6.9 per cent a year, girls 5.0 per cent a year

One apex to beyond second anterior rib boys, 9.3 per cent a year, girls, 7.2 per cent a year

Both apices to beyond second anterior ribs boys, 4.9 per cent a year, girls 13.2 per cent a year

#### PROGRESSIVE VERSUS RETROGRESSIVE LESIONS

Is it possible to foretell, once a lesion has been determined to be tuberculous, whether it will progress, retrogress or remain stationary? This is an important question in prognosis and when an attack upon an early lesion by collapse therapy is being considered. Lesions that tend to retrogress on the whole do well. Lesions that show steady progression, no matter how slowly, ultimately do poorly. This brings us face to face with the enigma of the shadow due to the primary infiltrate, which, on the whole, retrogresses, and the shadows due to secondary disseminations or reinfections which we have seen to progress in 2 out of every 3 cases. Unfortunately, from the X-ray appearance of the shadow itself, when not accompanied by definitely visible calcified tracheobronchial nodes, it cannot be ascertained in the first film whether the lesion is a primary infiltrate or a shadow due to a secondary dissemination or reinfection. When calcified tracheobronchial nodes either accompany or precede the soft shadow, it is usually certain at least that we are dealing with secondary dissemination or reinfection tuberculosis, but the behavior of the individual lesion can be determined only by serial films. In answering this question, then, there must be considered in addition to the character of the shadow certain other factors, namely,

the age of the patient, accompanying or preceding calcified tracheobronchial nodes and the tuberculin test

*A* Given a positive tuberculin test simultaneous with the discovery of the lesion

1 In the age group five to nine years, a soft sub- or infraclavicular shadow will as a rule behave like a primary infiltrate, will subside sooner or later, with or without treatment, and will usually leave in its place residual calcified nodes or strand-like shadows or both. No lesions of this character in boys were included in this study. The one lesion included was a girl, seven years of age, whose lesion, however, showed retrogressive changes at first, then began to progress and behave like an "adult-type" lesion. Apical lesions in the first decade of life, homogeneous in character and unaccompanied by calcified nodes, also tend to resolve (case 7, figures G and G<sub>1</sub>, plate 3). Apical lesions in this age group, soft in appearance and accompanied by calcified nodes, tend to spread and disseminate (case 3, figures C and C<sub>1</sub>, plate 1). Eight boys of this age group with apical lesions were included in this study. Of these, 5 had progressed with two deaths and 3 had retrogressed at the end of 6.5 mean years of observation. Of the 10 girls in the first decade of life with apical lesions, 5 had progressed with one death, 3 had retrogressed, and 2 remained stationary at the end of 6.7 mean years of observation. The rate of progression is extremely slow for the children in this age group.

2 In the second decade of life, soft lesions, subclavicular or apical, homogeneous or mottled, accompanied by calcified tracheobronchial nodes or not, will, in the majority of instances, progress, that is to say, two out of every three will progress (see plates 1, 2 and 3). The only way to determine their behavior is by serial X-ray films. A soft lesion may remain stationary for a time but this fact should not deceive us. These lesions should never be dismissed as clinically unimportant even in the absence of symptoms or signs.

*B* If the tuberculin test is known to be definitely negative immediately before the specific process in the lungs develops and becomes positive at the time of the discovery of the lesion, the shadow is due to the primary infiltrate in any age.

*C* A hard, strand-like or stringy shadow in any location will, with rare exceptions, remain stationary during puberty and may be dismissed as unimportant after puberty has passed.

# CHANGES WHICH OCCURRED IN THE GROUP AT THE END OF FOUR MEAN YEARS OF OBSERVATION

1 Two-thirds of the cases have progressed according to X-ray observation

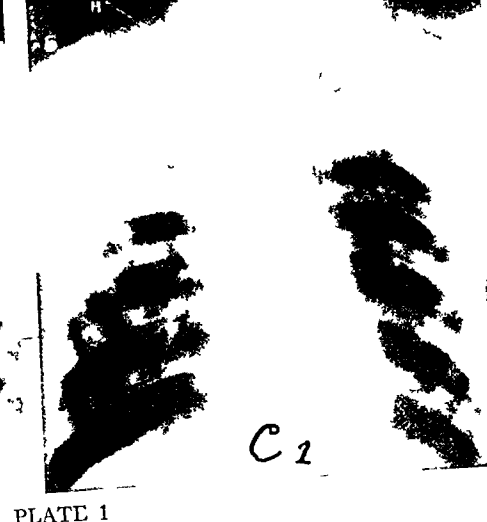
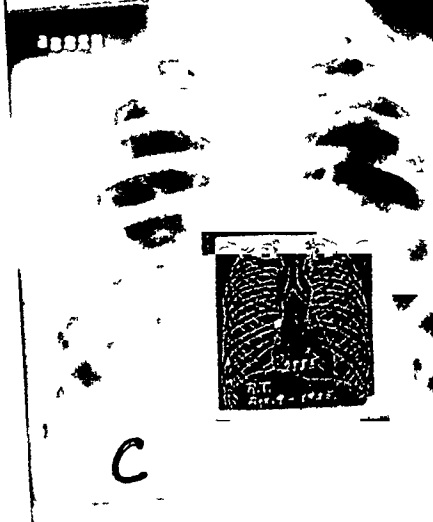
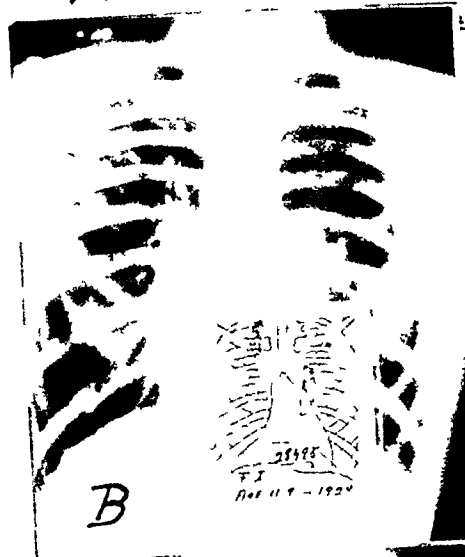
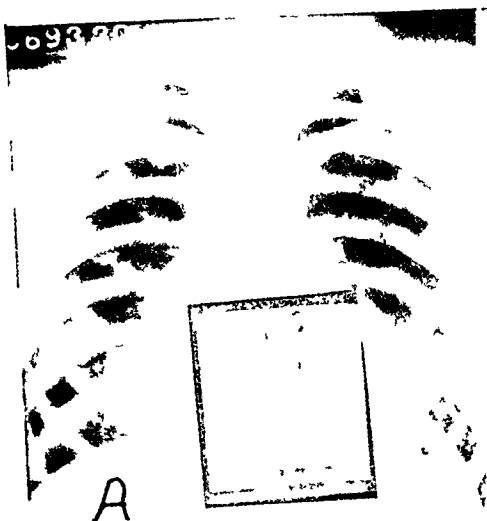
2 Of the patients with asymptomatic lesions 44.5 per cent have developed symptoms and/or signs. The average interval between the first X-ray film and appearance of clinical symptoms was three years. The rate of development was 10 per cent a year.

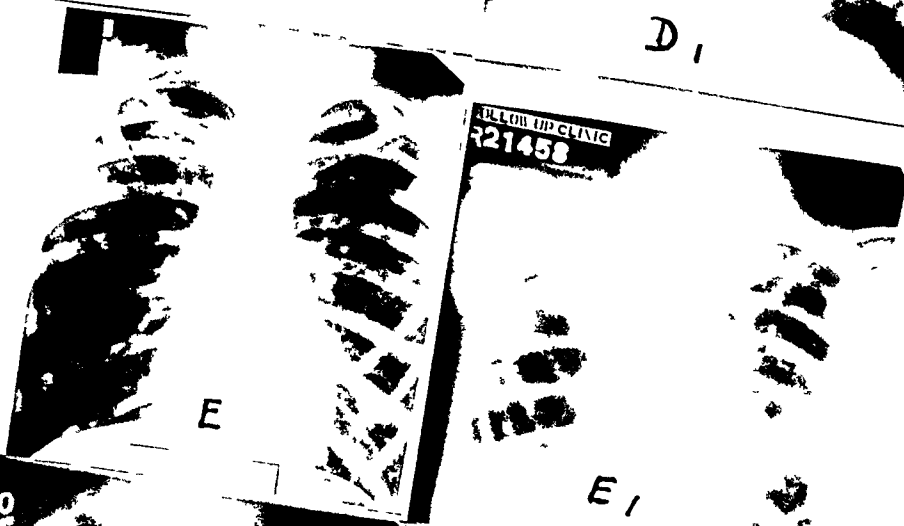
## PLATE 1

FIGS A & A<sub>1</sub> Progressive lesion. Case 1 R J M. Boy, thirteen years and four months old, weight 90 pounds, height 60 inches. Average weight Asymptomatic. Initial film A May, 1934. Calcified node right apex. Left apex, calcified node and homogeneous shadow occupying less than one half the apex above the first anterior rib. B<sub>1</sub> March, 1935, slow spread to third left anterior rib with small cavity in apex. Serial film A<sub>1</sub> February, 1936. Mottled shadow has extended through left lung field. Right top, calcified nodes as in 1934, but in addition a hazy shadow in extreme apex. Weight 120 pounds, height 66 inches. Became symptomatic in January, 1936, and sputum positive in March, 1936. From May to December, 1936 in sanatorium under collapse therapy.

FIGS B & B<sub>1</sub> Progressive lesion. Case 2 F I. Girl, eleven years and nine months old, weight 72 pounds, height 57 inches. Ten per cent underweight. Initial film B February, 1929. Homogeneous shadow occupying less than one half of right apex above clavicle, mesially, and along upper mediastinum to right of hilum, calcified nodes in right hilum. Left perihilar shadow with calcified and small calcified node in first left anterior interspace. By 1931 spread to second right anterior rib. Now rales and symptoms but consultant does not agree with sanatorium recommendation. From 1932 to 1934 slowly progressive lesion in right with cavity. In 1932 contralateral spread left top and left midlung. Weight 100 pounds in 1932, 109 pounds in 1934, then stationary. Serial film B<sub>1</sub> March, 1935. Bilateral disseminated coarse mottled shadows occupying more than two thirds of both upper lung fields. From April to September, 1936 in sanatorium under bilateral collapse. Denies symptoms and no sputum available for examination.

FIGS C & C<sub>1</sub> Progressive lesion. Case 3 T R. Boy, nine years and one month old, weight 55 pounds, height 49.6 inches. Average weight. Initial film C 1925. Homogeneous shadow both apices above first anterior ribs. Calcified node in right apex and two or three calcified nodes in right base. Left hilum moderately dense without definite calcification. Questionable calcified node in first left anterior interspace. From 1926 to 1928 refused examination because consultant gave an opinion that there was nothing clinically wrong with the boy at this time, the lesion at top of right lung being old and causing no symptoms, it is entirely inactive, no fever, no moisture. From 1929 to 1930 bilateral X-ray spread to second anterior ribs with small cavity in right apex and questionable cavity in first left anterior interspace. Serial film C<sub>1</sub> November, 1931. Coarse and fine mottled shadows in both lung fields to third anterior ribs, more marked on right. Cavity in first right anterior interspace. Question of cavity in first left anterior space. Weight 116 pounds, height 66.5 inches, seven per cent below average. Symptomatic with slight fever, 99.6° to 100.2° F, then rapid decline to October, 1932, when he died. Duration of life, seven years and four months.





F

F1

3 Of 65 boys who still remain symptom free, 33.8 per cent show progressive changes by X-ray. Of 127 girls who are still without symptoms, 41.7 per cent show progressive changes on serial films.

4 Of the whole group, 19.3 per cent have developed cavities, 15.6 per cent boys and 21.0 per cent girls.

5 Of the group who had no sputum or negative sputum at the time of the original diagnosis, 23.1 per cent have developed positive sputum in an average interval of 3.5 years after diagnosis.

6 Ninety-five girls and 27 boys have died from pulmonary tuberculosis, one boy died from another cause.

7 Of the boys, 74.5 per cent and of the girls, 68.3 per cent received sanatorium treatment.

#### PLATE 2

FIGS D & D<sub>1</sub>. Apical lesion, progressive. Case 4 J. E. Girl, fifteen years and seven months old, weight 120 pounds, height 62.5 inches. Five pounds above average. Asymptomatic. Initial film D, March, 1930. Mottled shadow left apex to second anterior rib. Calcified node in extreme apex. Calcified nodes in right hilum. July, 1930, in sanatorium, afebrile and gained in weight until early in 1931 when she began losing weight despite bed-rest. Toxic in May, 1931, with symptoms and positive sputum. Lesion to third left anterior rib with a cavity in first left anterior interspace. In July, 1931, haemoptysis. August, 1931, spread in right. Serial film D<sub>1</sub>, May, 1932. Bilateral coarse and fine mottling with large cavity in left first and second anterior interspaces. Died in July, 1932. Duration of life, two years and four months.

FIGS E & E<sub>1</sub>. Subclavicular lesion, progressive. Case 5 J. G. Girl, eleven years and eight months old, weight 68 pounds, height 57.5 inches. Fifteen per cent plus below average. Asymptomatic. Initial film E, April, 1931. Fine mottled shadow first and second right anterior interspaces. Calcified primary complex right hilum and along ninth posterior rib. Serial film E<sub>1</sub>, October, 1932. Right apex to third right anterior rib, mottling with cavity, trachea to right, slight atelectasis. Left infiltration in apex with questionable small cavity and fine mottled shadows in second, third and fourth left anterior interspaces. From December, 1932 to May, 1936 in sanatorium, gained to 99 pounds, always asymptomatic, but rales present in right. In July, 1934, right pneumothorax without result. Phrenicectomy in August, 1934. May 19, 1936, right thoracoplasty as left lesion retrogressed. Died on May 23, 1936. Duration of life, five years. (Note: This girl was under observation since eight years of age in 1928 for calcified primary complex.)

FIGS F & F<sub>1</sub>. Subclavicular lesion, retrogressive. Case 6 W. A. Girl, fifteen years and five months old, weight 102 pounds, height 63 inches. Ten per cent below average. Asymptomatic. Rales right top. Initial film F, June, 1929. Homogeneous shadow first and second right anterior interspaces. Calcified node in left apex and along ninth left posterior rib. From 1929 to 1933 in sanatorium off and on, always asymptomatic and sputum never positive. Lesion showed steady retrogressive change to calcification and fibrosis. Discharged as quiescent in April, 1933. Serial film F<sub>1</sub>, May, 1936. Calcified node in right apex, fine strand in right apex and first right anterior interspace. Calcified nodes along right tracheobronchial region. Calcified node in left apex and along left ninth posterior rib. Well.



8 Of the 141 living boys, 69 are still under treatment at sanatoria, 19 are unimproved at home, and 53 (37.6 per cent) are well. Of the 272 living girls, 97 are still under sanatorium treatment, 53 are unimproved at home and 122 (44.8 per cent) are well.

### MORTALITY

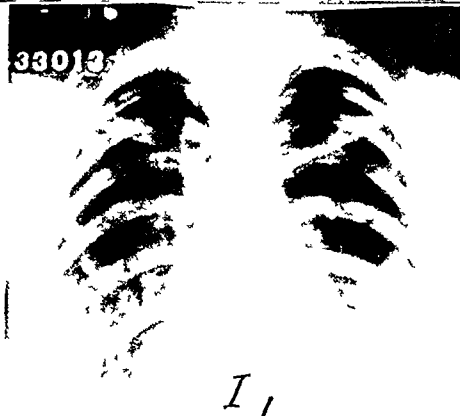
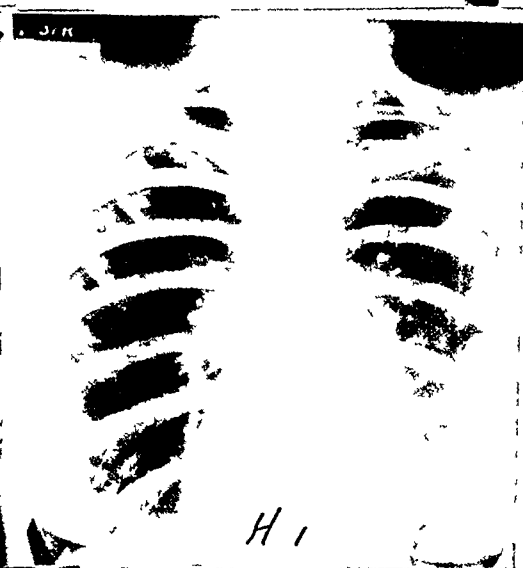
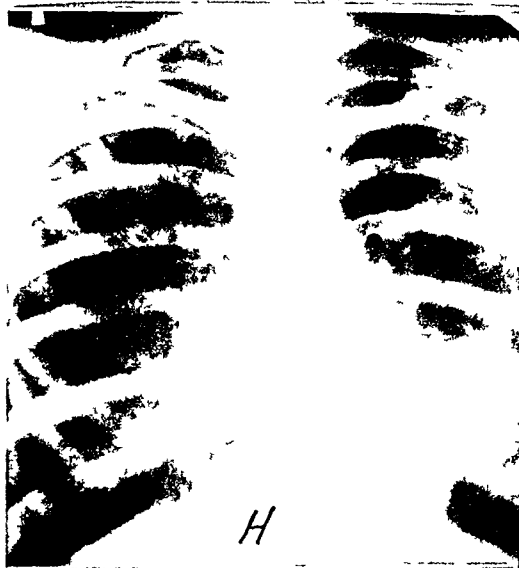
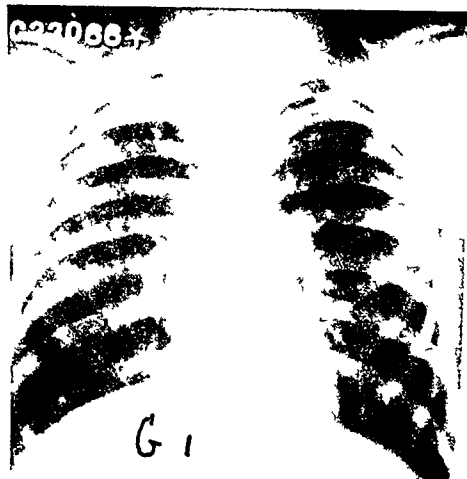
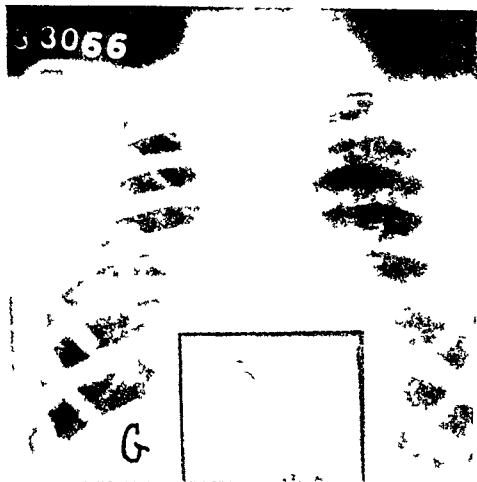
The case fatality of a chronic disease such as pulmonary tuberculosis cannot be expressed simply by stating the number of deaths as a percentage of the whole number, as it is correct to do for an acute disease, for example, lobar pneumonia. To determine the rate of mortality for pulmonary tuberculosis, a disease which must be observed for a long period of time, it is necessary to consider in the first place that the number available for calculations becomes less and less as time goes

### PLATE 3

**FIGS G & G<sub>1</sub>** Retrogressive lesion. Case 7 P. K. Boy, eight years and seven months old, weight 55.5 pounds, height 50 inches. Six pounds below average. Always delicate, "bronchitis" since birth. Initial film G, January, 1932. Homogeneous shadow in right apex to first anterior rib. No visible calcification. From March, 1932 to August, 1933 always afebrile and asymptomatic. Steady retrogressive change to late in 1933 when definite calcified nodes replaced the shadow seen in 1932. Lesion has remained stable to January, 1937, serial film G<sub>1</sub>. In school. Weight 79 pounds, height 59 inches. Ten per cent below average.

**FIGS H & H<sub>1</sub>** Retrogressive lesion. Case 8 K. J. Girl, fifteen years and two months old, weight 115.5 pounds, height 66.5 inches. Ten per cent below average. Asymptomatic. Initial film H, May, 1931. Coarse mottled shadow, right apex to third anterior rib. Irregular shadow left first and second anterior interspaces. Calcified nodes not visible. Highlight along fourth anterior rib left is blood vessel. From August, 1931 to February, 1936 in sanatorium. Slow steady retrogression. Steady gain in weight to 131 pounds. Always asymptomatic. Serial film H<sub>1</sub>, February, 1936. Strands with calcified spots in first right anterior interspace. Calcification in right hilum. Strands with calcified spots in left apex and first and second anterior interspaces. Is well and working.

**FIGS I & I<sub>1</sub>** Retrogressive lesion. Case 9 S. D. A. Girl, eleven years and four months old, weight 56 pounds, height 53 inches. Fifteen per cent below average. "Bronchitis" since birth. Rales in right apex. Initial film I, February, 1932. Homogeneous shadow, right apex to beyond second anterior rib, one or two small ring shadows in first right anterior interspace. No calcification visible. From April, 1932 to January, 1935 in sanatorium. Symptomatic with fever. Sputum positive once in April, 1932 and again May, 1933. Shadow began to show retrogressive changes in April, 1932 and became stabilized by 1935. Serial film I<sub>1</sub>, January, 1937. Stringy shadow in right apex. Heavy comet-like streak is the vena azygos usually seen in this position. Few strands in second right anterior interspace. Calcified node in right hilum. (Obliteration of left costophrenic angle was produced in reduction.) In school. Weight 101 pounds, height 61 inches. Ten per cent below average. Differential diagnosis: atelectasis and foreign body, upper lobe bronchiectasis, interlobar pleural effusion, and lung abscess.



DAVID ZACKS

J<sub>2</sub>



K<sub>2</sub>



PLAIL 1

K<sub>1</sub>



K



on, and, in the second place, that the patients came under observation in small numbers year by year and some are observed longer than others. For this reason the computations must be made step by step from year to year by actuarial methods. Mortality obtained in this way is spoken of as the cumulative mortality. To obtain a stable rate, the actuarial method requires a large number of cases, the larger the number, the more stable the rate. In the group under discussion, the number on which the mortality rate is based in each year is too small to give stable rates. However, the rates for the first year, the first five years, and the whole ten-year period, are significant and agree with actual clinical experience. The mortality is based on white children only.

The significant fact in table 3 is the delay in the cumulative mortality. The ultimate outcome in tuberculosis is uncertain during at least ten years of observation, especially for minimal lesions. For boys, the mortality at the end of five years' observation is 6.5 times that of the first year and at ten years, 12.8 times that of the first year. For girls the five year mortality is 7.4 times, and the ten year mortality is 17.4

#### PLATE 4

FIGS J, J<sub>1</sub> & J<sub>2</sub>. Progressive, then retrogressive lesion. Case 10 M J. Girl, eleven years and nine months old, weight 78 pounds, height 57.6 inches. Five per cent below average. Asymptomatic. Initial film J. March, 1927. Coarse mottled shadow in upper right mediastinum, extending into first and second right anterior interspaces. No calcification. December, 1929, age thirteen years and seven months, weight 100 pounds. In school with "herd cold," rales right top. Serial film J<sub>1</sub>. Homogeneous shadow with well defined lower margin and ring shadow in first right anterior interspace. From March, 1930 to February, 1933 asymptomatic. In State Sanatorium. Admission film (March, 1930) showed considerable clearing over that in December, 1929. Cavity not definitely visible. Gained weight to 130 pounds. Rales disappeared in November, 1932. February, 1933 apparently arrested. In 1936 well and working. Serial film J<sub>2</sub>. Discrete, sharp shadows, calcified, are all that remains in place of the extensive lesion seen in serial film J, December, 1929.

FIGS K, K<sub>1</sub> & K<sub>2</sub>. Retrogressive, then progressive lesion. Case 11 S P. Girl, five years and nine months old, weight 37.5 pounds, height 42.5 inches. Average weight. Asymptomatic. Initial film K. February, 1930. Homogeneous shadow left apex. No visible calcium. From 1930 to 1934 retrogressive changes with one or two calcified spots in the centre of lesion, this is not complete, however, since hazy shadow remains about the calcified core. Serial film K<sub>1</sub>. June, 1934 to May, 1935, slight spread to first left anterior interspace. Weight stationary at 70 pounds. Height stationary at 53 inches. Asymptomatic. Lesion continued to spread slowly though weight increased. Serial film K<sub>2</sub>. May, 1937. Fine to coarse mottled shadow throughout left lung field. Small cavity left apex. (Fine mottled shadow in second right anterior interspace.) Age thirteen years, weight 94 pounds, height 59 inches. Average weight 92 pounds. Is symptomatic.

times that of the first year. The mortality was also calculated for the special groups shown below with the following results:

Positive sputum cases, cavity cases and cases showing X-ray progression give a consistently high mortality with or without treatment.

The mortality rate for open cases is 7.4 per cent a year for boys and 12.5 per cent for girls.

The rate for cavity cases is 8.4 per cent a year for boys and 14.0 per cent for girls.

The rate for progressive lesions according to X-ray observation is 6.7 per cent a year for boys and 11.4 per cent for girls.

TABLE 3

*Cumulative mortality from pulmonary tuberculosis during various time periods after discovery of disease in 169 boys and 367 girls, according to age groups in years when diagnosis was first made\**

AGE GROUP	NUMBER OF CHILDREN		DEATHS FROM PULMONARY TUBERCULOSIS											
			Within one year				Within five years				Within ten years			
	M	F	M	Per cent	F	Per cent	M	Per cent	F	Per cent	M	Per cent	F	Per cent
<i>years</i>														
0-9	8	11	0	0	0	0	1	13.3	0	0	2	56.6	0	0
10-14	64	144	0	0	2	1.4	8	16.4	30	28.7	11	36.4	45	67.4
15-23	97	212	5	5.4	11	5.5	14	21.5	40	26.7	14	21.5	50	64.6
Total	169	367	5	3.0	13	3.7	23	19.5	70	27.3	27	38.8	95	64.4

\* Basic table showing steps in calculation from year to year is not given. The method used is the common life experience and mortality tables used in actuarial computation.

Boys with positive sputum have 3 times the mortality of closed cases, girls with positive sputum have over 3.5 times the mortality of closed cases.

There was no significant difference in mortality between contact and noncontact groups (contact boys, 3.8 per cent a year, noncontact boys, 4.5 per cent a year, contact girls, 6.9 per cent a year, noncontact girls, 5.6 per cent a year).

Pulmonary lesions accompanied or preceded by calcified tracheo-bronchial nodes show a slightly, but not significantly, lower mortality for boys (boys with calcified nodes, 3.8 per cent a year, boys without such nodes, 4.1 per cent a year). For girls, the mortality of pulmonary lesions accompanied or preceded by calcified nodes was 5.5 per cent a year, against 9.0 per cent a year when calcified nodes were absent in the

film. This fact would suggest a lesser resistance to the inroads of the disease in the group of girls without calcified nodes.

#### DURATION OF LIFE

Table 2 shows that the death rate is directly proportional to the extent of the lesion at the time of diagnosis. It appears further that the duration of life in morbid cases has an inverse relationship to the age at diagnosis as well as to the extent of the lesion. For the age group five to nine years, the duration of life was 6 years, for the age group ten to fourteen years, 5 years, for the age group fifteen or more years, 3 years. Does this mean that the lesions when found were more advanced in the older age groups, or does a lesion spread more rapidly when acquired in mid or late puberty? The data presented earlier (table 1) would indicate that the lesions were more advanced in the older age groups. This fact, however, is not the entire explanation. Age *per se* is also a factor to be reckoned with. For it was found that for lesions of similar extent the duration of life is shorter, the older the patient at the time of diagnosis. For minimal lesions, the duration of life for the age group five to nine years was 6 years, for the age group ten to fourteen years 5.3 years, for the age group fifteen or more years, 4.1 years. For advanced lesions, the duration of life for the age group ten to fourteen years was 3.6 years, and for the age group fifteen or more years, 2.3 years. It is noteworthy that the sexes show very little difference in the duration of life in morbid cases.

#### SUMMARY

A group of 536 children with pulmonary tuberculosis, the majority in the second decade of life, diagnosed by X-ray in the great majority of instances, was observed carefully an average of four person years. The course of the early, minimal, asymptomatic lesions was traced and the behavior of the individual lesions was discussed. It was shown that within the period of observation two-thirds of the lesions have progressed according to X-ray observation, when symptoms, cavities and positive sputum developed and their rate of development per hundred person years was calculated. Roentgenograms were presented to illustrate the courses of the early lesions in the spreading and retrogressive phases. The cumulative mortality for such a group was calculated for the first year, the first five years and the entire period of observation.

## CONCLUSIONS

Tuberculous disseminations or reinfections in the second decade of life begin as minimal lesions early in the decade, spread slowly in the majority of instances by contiguity as time goes on, and show no symptoms or at most imperceptible symptoms at first. With the arrival of mid or late puberty, the lesions have advanced to such an extent as to give symptoms referable to the chest or toxic symptoms. The diagnosis is usually made with the advent of symptoms, unless the lesions are discovered earlier by routine X-ray examination of tuberculin-positive children. In the great majority of instances, these lesions will be found in the apices. These asymptomatic X-ray lesions, once they have been differentiated from similar nonspecific lesions which may mimic them, should be regarded as of grave import. Asymptomatic lesions, when soft in appearance, show in general two distinct phases of behavior according to serial X-ray films, one type shows a tendency to spread, the other to retrogress. This behavior, unfortunately, cannot be foretold by the X-ray appearance of the initial lesion. The progressive lesions may spread slowly or rapidly, and will kill the great majority of patients within ten years, the duration of life depending inversely upon the extent of the lesion and the age at the time of diagnosis. The retrogressive type of lesions tends to subside during a longer or shorter interval of time, and the patient will survive puberty, the critical period for this group of patients.

The subclavicular or infraclavicular lesions show the greatest proportion of spread and the highest cavity rate for lesions of minimal extent. Toxic symptoms are of prognostic rather than diagnostic significance in this age group.

Although the incidence of pulmonary tuberculosis is twice as high in girls of this age, the subsequent course of the disease and the case fatality is essentially the same as in boys.

I wish to thank the Clinic Clerks, Miss Riordan, Miss Block, Miss Marquis and Miss Morrissey, for their help in the preparation of this paper, Miss Hamblen, our Statistician, for her work in checking the tables and estimating their significance, Dr H. D. Chadwick, Dr A. S. Pope and Dr Roy Morgan, for their patience and kindness which made this study possible.

# PULMONARY TUBERCULOSIS IN THE SECOND DECADE OF LIFE<sup>1</sup>

## II Its Treatment and Prognosis

DAVID ZACKS

In a previous communication (1) the development and fatality of pulmonary tuberculosis in the second decade of life were discussed. In this paper will be considered its treatment and its prognosis as measured by X-ray observation. The study is based on 536 children with pulmonary tuberculosis who were followed an average of four years. The longest period of observation was twelve years, the shortest was one year. The clinical status of the treated and untreated boys and girls at the end of the follow-up period is given in table 1.

The most pertinent observation in table 1 is the slightly greater mortality in the treated than in the untreated boys and girls. The treated boys give a mortality rate of 4.2 per cent a year, the untreated 3.2 per cent a year. The mortality for the treated girls is 7.1 per cent, the untreated 5 per cent. This result can be explained only on the basis of selection as the more advanced cases were naturally the first to accept treatment.

### TREATMENT

Treatment for pulmonary tuberculosis might be expected to do two things—it might at least prolong the life of the patient or it might at most assist nature to arrest the progress of the disease. An accurate appraisal of the result of any method of treatment must be based on not less than ten years of observation. In Massachusetts, until 1932, treatment for children in the second decade of life was bed-rest at a sanatorium. The rest treatment, until 1927, was of short duration, or in febrile patients as long as the fever continued. Beginning in 1927, one year of bed-rest was routine treatment for all children with pulmonary infiltrations regardless of extent.

*Treatment by bed-rest alone.* Patients with pulmonary tuberculosis in

<sup>1</sup> From the Massachusetts Department of Public Health, Boston, Massachusetts.



TABLE 1

*Status of 160 boys and 367 girls at the end of the follow-up period after treatment per person years of observation*

SEX	TREATED		UNTREATED		TOTAL	
	M	F	M	F	M	F
Number of persons	126*	252†	13	115	169	367
Per cent of persons	71.5	68.7	25.4	31.3	100.0	100.0
Treatment years	262.0	190				
Person years observation	517	1,033	157.5	436.5	674.5	1,169.5
Mean person years	4.1	4.1	3.7	3.8	4.0	4.0

Result at the end of the follow-up period

Number dead	22	73	5	22	27	95
Per cent dead	17.5	28.9	11.6	19.1	16.0	25.9
Death per 100 person years	1.2	7.1	3.2	5.0	4.0	6.5
Number living	104	179	37‡	93	141‡	272
Per cent living	82.5	71.0	86.0	80.9	83.4	74.1
Number at sanatorium	65	81	0	0	65	84
Per cent at sanatorium	62.5	16.9	0	0	46.1	30.9
Number unimproved	9	16	10	37	19	53
Per cent unimproved	8.6	8.9	27.0	39.8	13.5	19.5
Number well and reported well	27	73	26	19	53	122
Per cent well and reported well	26.0	10.8	70.3	52.7	37.6	44.8
Number with home treatment	0	3	1	7	1	10
Per cent with home treatment	0	1.7	2.7	7.5	0.7	3.7
Number O P D pneumothorax	3	3	0	0	3	3
Per cent O P D pneumothorax	2.9	1.7	0	0	2.1	1.1

\* Boys

55 Sanatorium only

71 Sanatorium with surgical procedure

46 Pneumothorax only

4 Pneumothorax with thoracoplasty (1 also phrenicectomy)

4 Pneumothorax with pneumonolysis

6 Pneumothorax with phrenicectomy

8 Phrenicectomy only

3 Thoracoplasty only (2 had phrenicectomy)

† Girls

132 Sanatorium only

120 Sanatorium with surgical procedure

75 Pneumothorax only

6 Pneumothorax with thoracoplasty (3 phrenicectomy)

10 Pneumothorax with pneumonolysis (1 phrenicectomy)

17 Pneumothorax with phrenicectomy

11 Phrenicectomy only

1 Thoracoplasty only (1 phrenicectomy)

‡ One (1) boy died of other causes

the advanced or moderately advanced stages, according to the accepted classification, were naturally the first to accept sanatorium treatment. When the child was objectively ill there was no question as to the necessity for treatment either by the child's family or by the family physician. Unfortunately, bed-rest alone for shorter or longer periods, judged by the ten-year standard, has failed utterly to influence the course of the disease. This statement is not only true for the advanced positive sputum cases, but is also true for minimal cases that progress according to X-ray observation.

Morgan (2) wrote in 1934 that the vast majority of positive sputum cases will be lost even if given prolonged bed-rest. Klare (3) in Germany,

TABLE 2  
*Mortality rates for treated and untreated special groups*

	NUMBER		MEAN PERSON YEARS		PER CENT DEAD		DEATH RATE PER 100 PER YEAR	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Total								
Treated	126	252	4.1	4.1	17.5	28.9	4.2	7.1
Untreated	43	115	3.7	3.8	11.6	19.1	3.2	5.0
Open cases								
Treated	50	117	3.8	3.9	28.0	47.0	7.4	12.0
Untreated	0	10	0	3.6	0	70.0	0	19.5
Cavity cases								
Treated	40	101	3.6	3.9	30.0	52.5	8.3	13.4
Untreated	3	18	3.2	3.9	33.3	66.7	10.5	17.1
X-ray progressive lesions								
Treated	95	166	3.7	3.8	23.2	43.9	6.2	11.6
Untreated	16	63	2.8	3.2	31.2	34.9	11.1	10.8

reporting in 1936 on a series of 502 open cases in children and youths followed ten years or more, found a mortality of 95.5 per cent with 4.5 per cent able to work. This mortality was the same for boys and girls. Cochrane (4), in England, in 1935 reported a mortality of 74.9 per cent for boys and 71.3 per cent for girls in sanatorium treated open cases that were discharged during the years 1922 to 1929. Our experience with open cases, with cavity cases and with minimal lesions that showed progression by X-ray under observation is given in table 2.

This table shows a striking mortality for the treated as well as the untreated groups. In the open cases the treated boys gave a mortality of 7.4 per cent a year and the girls 12 per cent a year. The cavity cases

showed a mortality of 8.3 per cent a year for the treated boys and 13.4 per cent a year for the treated girls. Lesions that showed progression by X-ray are not far behind with a mortality of 6.2 per cent a year for the treated boys and 11.6 per cent a year for the treated girls. Of the 50 treated boys with open lesions, 31 had pneumothorax (2 with pneumonolysis), 4 had thoracoplasty (2 with phrenic interruption) and 8 had phrenicectomy only. Of the 117 treated girls with positive sputum, 72 had pneumothorax (4 with pneumonolysis, 1 also with phrenic interruption), 5 had thoracoplasty (3 with phrenic interruption), and 19 had phrenicectomy only. Details of treatment for cavity cases are given in table 5.

*Bed treatment in progressive lesions.* In our experience, bed-rest alone in a sanatorium does not modify the course of spreading tuberculous lesions to an appreciable degree and does not reduce the mortality for these lesions. This statement is supported by the data in table 3.

In this table, treatment refers to all forms of treatment, namely, bed-rest at sanatorium, pneumothorax and other surgical procedures. Early treatment refers to treatment instituted within one year of diagnosis. Later treatment means active treatment begun one or more years after diagnosis. For the purpose of this analysis 158 children who received no treatment were combined with 114 who received later treatment. No difference was observed in the early treated group as against the untreated or later treated group in the proportion of spread. The group with early treatment shows a slightly better but not significantly better mortality than the untreated group. The group that showed spread by X-ray despite early treatment had a mortality of 32.8 per cent after four years of observation, against a mortality of 38.9 per cent for the non-treated group, not a significant difference.

The significance of asymptomatic minimal lesions was not fully and generally appreciated, even by tuberculosis specialists until comparatively recently, paradoxical as this may sound. This ignorance was general and was due to a lack of sufficient experience with these lesions and consequently an unwillingness to make a diagnosis, to say nothing of recommending treatment on X-ray evidence alone. For many years the cry had been, "Find the early cases!" When a method had been elaborated whereby the really early lesions were discovered by the use of the tuberculin test and the X-raying of reactors, we did not know how to treat these lesions, or indeed, whether treatment was necessary. In the absence of symptoms and signs, these early X-ray lesions were pre-

maturely labeled "latent," a term which was generally taken to mean "inactive" or "healed." It was said that we had better wait until the lesions had become "manifest," that is, had physical signs such as râles, and symptoms referable to the chest. It has required time to demonstrate the potential danger of these innocent and insignificant looking lesions.

TABLE 3

*X-ray at the end of the follow up period for 536 pulmonary cases according to treatment after 2.44 person years of observation*

RELATION OF TREATMENT TO END RESULT BY X RAY	TOTAL NUMBER 536 MEAN YEARS, 4.0		X RAY RESULT AT THE END OF THE FOLLOW UP PERIOD							
			Progressed 340 (63.4%)		Retrogressed 129 (24.1%)		Stationary 37 (6.9%)		Unknown 30 (5.6%)	
	With early treat- ment	With- out or with later treat- ment	With early treat- ment	With- out or with later treat- ment	With early treat- ment	With- out or with later treat- ment	With early treat- ment	With- out or with later treat- ment	With early treat- ment	With- out or with later treat- ment
Number of children	264	272	168	172	74	55	19	18	3	37
Percentage of change			63.6	63.2	28.0	20.2	7.2	6.6	1.1	9.9
Per cent dead after 4 mean years	20.8	24.6	32.8	38.9	0	0	0	0	0	0
Boys										
Total number boys 169	88	81	62	49	20	16	5	5	1	11
Mean years 4.0			70.5	60.5	22.7	19.7	5.6	6.2	1.1	13.6
Percentage of change										
Per cent dead after 4 mean years	14.6	17.3	21.0	28.6	0	0	0	0	0	0
Girls										
Total number girls 367	176	191	106	123	54	39	14	13	2	16
Mean years 4.0			60.2	64.4	30.7	20.4	8.0	6.8	1.1	8.4
Percentage of change										
Per cent dead after 4 mean years	23.9	27.7	39.6	43.1	0	0	0	0	0	0

Nevertheless, some of these early lesions were hospitalized after a great deal of effort in persuading the family physicians and indeed the tuberculosis specialists that treatment was indicated. The treatment consisted of short periods of bed-rest and, when this failed, to prevent readmissions a longer period of bed-rest was given without any better results. Time and again, when soft lesions remained stationary, as

they will do for some time, the patients were discharged as "arrested" because there were no symptoms and the weight and general condition had improved under bed-rest. The patients, however, usually returned with the lesion more extensive than before. The lesions that retrogressed as shown by X-ray did well with bed-rest, as they usually will without any treatment at all. The lesions that spread continued to spread despite periods of bed treatment. Morgan (2) in 1934 stated, "The end results in the incipient and moderately advanced cases seem about the same (in mortality) although the incipient did better for a time. This can probably be explained by the fact that we did not take these incipient cases seriously enough and discharged them too early." (See table 3.) Bed treatment was in vogue at Westfield Sanatorium until 1932 when pneumothorax treatment came into more general use.

*Sanatorium plus pneumothorax treatment* Pneumothorax treatment judged over a period of ten years has not benefited the course of the disease in the advanced stages to any appreciable extent. Klare (3) reports a mortality after ten years of 90.9 per cent with 9.1 per cent able to work. His mortality was the same for boys as for girls. Our experience with collapse therapy according to the topography of the lesions is given in table 4.

The most that can be said, perhaps, for this form of treatment in advanced bilateral lesions is that it tends to prolong life. The mortality for all bilateral lesions in girls is 12.9 per cent a year for bed treatment only, and 11.2 per cent a year for collapse therapy. For boys with bilateral lesions, the mortality for sanatorium treatment is 8.8 per cent a year and for pneumothorax 7.1 per cent a year. A better result is indicated for all unilateral lesions in girls, especially for the subclavicular and minimal apical lesions. The result with collapse therapy for unilateral lesions in boys is rather significantly better. Table 4, moreover, is not offered as a final answer to the benefit of really early collapse on minimal lesions. The lesions given in this table are the lesions as found at the time of diagnosis, but the collapse in the majority of instances was not applied soon after the diagnosis was made. This procedure is of more recent development. The tendency in most instances had been to treat first by bed-rest alone and then, if a definite spread occurred, by collapse. The table does show what to expect from pneumothorax for advanced lesions and lesions discovered early but allowed to progress too far before collapse is instituted.

Our experience with collapse therapy in cavity cases is given in table

TABLE 4  
Comparison in end results between sanatorium treatment only and sanatorium treatment plus pneumothorax treatment, by sex and topography of X-ray lesions, in mean years of observation

TOPOGRAPHY OF X-RAY LESIONS AT TIME OF DIAGNOSIS	BOYS										GIRLS					
	Sanatorium only					Sanatorium + pneumothorax					Sanatorium only			Sanatorium + pneumothorax		
	Number	Mean years observation	Per cent dead	Death rate per 100 per year	Number	Mean years observation	Per cent dead	Death rate per 100 per year	Number	Mean years observation	Per cent dead	Death rate per 100 per year	Number	Mean years observation	Per cent dead	Death rate per 100 per year
Subclavicular Lesions	2	2 0	0	0	11	3 7	0	0	13	4 1	38 5	9 3	16	3 6	12 5	3 4
Unilateral																
Apex above clavicle	11	5 7	9 1	1 6	12	4 3	0	0	31	4 4	16 1	3 7	18	3 9	11 1	2 9
Apex to second anterior rib	10	5 0	40 0	8 0	7	4 9	0	0	25	4 9	12 0	2 5	19	4 7	15 8	3 3
Apex to beyond second anterior rib	3	6 8	33 3	4 9	9	2 9	11 1	3 8	13	4 6	61 5	13 4	13	4 0	30 8	7 6
Unilateral with cavity	2	3 0	50 0	16 7	2	2 0	0	0	6	4 0	33 3	8 3	13	2 2	15 4	7 0
All Unilateral Lesions	26	5 3	26 9	5 0	30	3 9	3 3	0 9	75	4 5	24 0	5 3	63	3 8	17 5	4 6
Bilateral																
Apices above clavicles	13	4 7	7 7	1 6	5	5 3	0	0	13	6 4	15 4	2 4	5	3 7	40 0	10 8
Apices to second anterior ribs	6	5 5	50 0	9 1	4	4 0	25 0	6 3	9	4 1	44 4	11 0	5	5 9	40 0	6 8
Apices to beyond second anterior ribs	3	2 8	100 0	35 3	2	1 5	50 0	33 3	12	3 0	75 0	25 0	4	4 0	50 0	12 5
Bilateral with cavity	5	2 1	60 0	28 6	7	1 5	28 6	19 1	9	1 6	77 8	48 3	15	2 9	40 0	13 8
All Bilateral Lesions	27	4 2	37 0	8 8	18	3 1	22 2	7 1	43	4 0	51 2	12 9	29	3 7	41 4	11 2
Total Lesions	55	4 7	30 9	6 6	59*	3 6	8 5	2 3	131†	4 3	34 4	8 0	108	3 8	23 1	6 2

\* One boy not included because location and extent of original X-ray lesion unknown

† One girl not included because location and extent of original X-ray lesion unknown

5 The mortality for the cavity group as a whole is consistently very high, but for the same period of observation collapse therapy gives an immediately better result. The boys with collapse therapy have one-third the mortality, the girls one-half the mortality of bed rest only. Of the 19 boys with bed treatment, 3 had phrenicectomy, 1 had thoracoplasty and 2 had phrenicectomy and thoracoplasty. Of the 15 girls with bed treatment, 3 had phrenicectomy and 1 had phrenicectomy and thoracoplasty. Of the 21 boys with pneumothorax, 3 also had phrenicectomy, 3 had thoracoplasty (1 also had a phrenic interruption)

TABLE 5  
*Indirectly treated*

Sex	Boys			Girls			Total	
	Bed only	Bed with phrenicectomy	Total	Bed only	Bed with phrenicectomy	Total	Unresected	Operated
Number	19	21	40	15	56	101	3	18
Person years	70.5	74.5	145	181.5	215.0	396.5	9.5	70.0
Mean person years	3.7	3.6	3.6	4.0	3.8	3.9	3.2	3.9

Result at end of follow up period

Number dead	9	3	12	33	20	53	1	12
Per cent dead	47.4	14.3	30.0	73.3	35.7	52.5	33.3	66.7
Deaths per 100 per year	12.8	4.0	8.3	18.2	9.4	13.4	10.5	17.1
Number living	10	18	28	12	36	48	2	6
At sanatoria	7	16	23	6	30	36		
At home unimproved	1		1	3	3	6	2	6
Well and reported well	2	1	3	3	2	5		
OPD pneumothorax		1	1		1	1		

2 had pneumonolysis. Of the 56 girls with pneumothorax, 7 had phrenicectomy, 4 had thoracoplasty (2 also had a phrenic interruption), 3 had pneumonolysis and 1 had pneumonolysis and phrenicectomy. The great majority of the surviving boys and girls are still under treatment, however, with the ultimate outcome still problematical. It is noteworthy that only 8 patients out of a total of 162 are well.

The real question as to whether an early attack by collapse therapy on an early lesion will actually prevent the spread of the lesion and arrest the course of the disease remains unanswered. This problem is now being studied. Another five years will be necessary before a preliminary

report can be made. We need a standard by which to judge adequately this method of treatment. Some lesions we have seen to retrogress without treatment, others have progressed despite treatment. We must first ascertain whether we are collapsing the progressive type of lesion and then we must find the optimum period for collapsing a lesion. These are all questions for the future.

*Thoracoplasty* In this series, there were 14 thoracoplasties of various stages (7 boys and 7 girls). Of the total number, 10 had preliminary pneumothorax of long or short duration, and of the remaining 4, 3 had preliminary phrenics. There was one operative death among the girls. Of the boys, after 6.5 person years of observation (three person years after the surgical operation) 4 are still in sanatoria doing well and 3 have been discharged and are well. Of the 6 living girls after 6.5 person years of observation (approximately two person years after the surgical operation) 3 cases are still at sanatoria, 2 in fair condition, 3 have been discharged and are well.

As indicated, the result with thoracoplasty on the whole, although the number is small, is better than with pneumothorax, but this is probably largely a matter of selection. Nevertheless, in properly selected cases, thoracoplasty should not be deferred on account of the age of the patient, granted that the case selection for this procedure is definitely limited in this age group.

#### SUGGESTED PROCEDURE WITH COLLAPSE THERAPY

A hard and fast rule cannot be given as to procedure with pneumothorax treatment in the individual case. The following general suggestions may be found helpful.

In the age group five to nine years, chronic subclavicular infiltrations should be treated by bed-rest alone.

In older age groups, attack immediately cavity cases and apical lesions beyond the second anterior ribs. For subclavicular processes, allow a month or two in bed for observation by frequent serial films to determine whether the lesion shows definite retrogressive changes. If definite retrogressive changes do not occur, if the lesions remain stationary or show a tendency to spread no matter how slight, attack at once. An exception to this rule is perihilar or peritracheal infiltrates when observed during their spreading phase (formation of secondary infiltrates) which should not be collapsed immediately as these lesions will probably undergo spontaneous retrogressive changes. Apical lesions not greater in



extent downward than the second anterior ribs should be given a period of three to six months' observation in a sanatorium by serial films. If the lesions do not show a tendency to retrogress at the end of the period, then attack by pneumothorax. If adhesions hamper a good collapse, these should be surgically severed without waiting too long and the pneumonolysis should be done as thoroughly as possible to give the desired result. Pneumothorax should not be carried on too long for extensively adherent apical lesions that cannot be severed by pneumonolysis, as thoracoplasty is a much better procedure for these cases and will often avoid purulent exudates.

#### PROGNOSIS FROM X-RAY POINT OF VIEW

The prognosis is good for sub- or infraclavicular infiltrative lesions in the first decade of life. These lesions as a whole behave like primary infiltrates in that they subside sooner or later, with or without treatment, and leave in place of the infiltrate residual calcified nodes or strand-like shadows or both. Soft apical infiltrations in the first decade of life are rare, but when they occur the prognosis is good if the lesions are unaccompanied by calcified tracheobronchial or parenchymal nodes. These children, however, should be followed after the lesions have subsided with yearly X-ray examinations through puberty. Apical lesions in the first decade of life accompanied or preceded by calcified nodes will behave like similar lesions in the second decade of life.

In the second decade of life the prognosis for soft early lesions is uncertain for at least ten years. In general it may be said that the prognosis is directly related to the extent of the apical lesions in relation to the anterior or posterior ribs. Extensive lesions beyond the second anterior ribs, cavity cases and sputum positive cases, have a poor prognosis. Recoveries may occur but they are rare. When advanced lesions are accompanied by toxic symptoms, the prognosis is usually immediately hopeless. In individual cases, more important than the extent of the lesion is the behavior noted by serial X-ray films. Lesions that progress, no matter how slowly, ultimately do poorly. Retrogressive lesions should be observed until they are definitely stabilized as indicated by fibrous strands, by calcification or by both. Subclavicular lesions that retrogress have a good prognosis—the reverse is true if they progress. A stationary lesion when soft in appearance, homogeneous or mottled, has an uncertain prognosis. It is best not to temporize too long with these lesions. A stationary lesion, definitely strand-like or stringy, with

or without calcified spots, has a good prognosis. This type of lesion should, however, be observed through puberty, particularly in girls.

#### CONCLUSIONS

1. Bed-rest alone in a sanatorium does not modify the course of spreading tuberculous lesions to an appreciable degree and does not reduce the mortality of these lesions.

2. Therapy, either bed-rest alone or bed-rest with pneumothorax, has not affected to any appreciable degree the mortality in advanced bilateral lesions, or lesions of minimal extent that are allowed to progress too far without early attack by collapse therapy. Collapse therapy in advanced unilateral lesions tends at least to prolong life and it may be demonstrated by further observation that it also reduces the mortality.

3. Some evidence has been presented which would seem to indicate that an early attack by collapse therapy may reduce the fatality rate of early asymptomatic lesions that show a tendency to spread. A final answer on this point cannot be given without at least five more years of observation.

4. In the second decade of life, the prognosis for soft early lesions is uncertain for at least ten years. In individual cases, most important in prognosis is the behavior of the lesion according to serial X-ray films. Lesions that progress ultimately do poorly—those that retrogress on the whole do well.

5. Retrogressive lesions should be observed by serial films until definite stabilization is evident either by calcification or strand-like fibrosis or both.

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## DIABETES AND PULMONARY TUBERCULOSIS<sup>1</sup>

With Special Reference to the Lipid Content of Diabetic Lungs

HOWARD F ROOT AND WALTER R BLOOR

The peculiar relationship of diabetes and tuberculosis has been frequently studied since Avicenna (980–1027) commented upon phthisis as a frequent complication of diabetes. Lieutaud (1779), in a collection of several hundred autopsies, recorded cases of diabetes and phthisis, and John Rollo in 1798 described both clinical and postmortem records of cases of diabetes evidently complicated with pulmonary tuberculosis with cavitation. During the latter half of the nineteenth century the diabetic patient appeared doomed to die of pulmonary tuberculosis if he succeeded in escaping coma. Indeed, Bouchardat in 1883 stated in his text that at autopsy every case of diabetes had tubercles in the lungs. In the twentieth century, the association of the two diseases still occasions concern because of its great frequency, particularly in diabetic clinics of the great European cities where overcrowding and poverty insure the spread of tuberculosis. In Labbé's large hospital clinic pulmonary tuberculosis caused 40 per cent of the deaths in 1930, 1931 and 1932 (1), although in private cases the percentage is much more nearly like that of our own population. In any discussion of the frequency of pulmonary tuberculosis in diabetes, one must always bear in mind the effect of varying social conditions, types of population, the hospital from which the statistics are drawn and the type of diabetic treatment.

We have analyzed the records of tuberculosis occurring in 364 diabetic patients, of whom 119 are cases newly discovered, since 245 cases were described in 1934 (2). These 245 cases occurred among 9,592 true diabetics (among 11,023 glycosurics seen between 1898 and May 1, 1932) and 77 of these cases were discovered among 5,480 cases between May, 1932 and January 31, 1938. In the latter period naturally a large number of patients are included whose diabetes is still of short duration.

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A better comparison would be the ratio of cases to the total number of years of diabetes lived by all patients during the two periods. From this series certain facts are outstanding:

- 1 The development of pulmonary tuberculosis in juvenile diabetics, or in patients whose diabetes began at or before the age of twenty, occurs more than twelve times as frequently as among all pupils in Massachusetts' grade and high schools. Forty per cent of deaths in diabetic children, with diabetes of more than ten years' duration, were due to tuberculosis.
- 2 Between 1923 and 1929 pulmonary tuberculosis developed in 8 per cent of 105 diabetic patients within three years of recovery from coma. Among 97 patients treated for coma between February, 1929 and November, 1932, 24 died of other causes within a year or two. Of the 73 patients remaining, 13 have developed tuberculosis within five years.
- 3 The incidence of pulmonary tuberculosis in adult diabetics does not show a decrease in rate corresponding with the general decrease in tuberculosis mortality in the community, for which fact explanation may be sought in the increasing longevity of the diabetic and prolongation of the period of exposure to tuberculosis.
- 4 In 83 per cent of the cases, the development of tuberculosis appeared to follow the onset of diabetes. In 2 per cent accurate data regarding times of onset are lacking. In 15 per cent earlier pulmonary tuberculosis had apparently been arrested (by sanatorium or other treatment) only to be reactivated after onset of diabetes.

#### INCIDENCE

To gain an impression of the incidence of tuberculosis in diabetic patients, one must consider autopsy as well as clinical statistics. Autopsy data are difficult to interpret (1) because, in such series, the effect of prolonged duration of diabetes has not been given sufficient weight. A review of the literature reveals the fact that, in a great majority of autopsies on diabetics, the duration of diabetes was less than five years. Nowadays, with modern insulin treatment, we expect the average young diabetic patient to live many years longer. Certainly, if diabetes does influence the development of tuberculosis, diabetes of one or two years' duration is too short an exposure to affect the patient's chance to develop tuberculosis. (2) In any large autopsy series, the frequency of association of tuberculosis with any chronic disease is much less than the incidence of tuberculosis in the group as a whole. Thus, we should compare the frequency of tuberculosis in diabetic patients with the frequency of tuberculosis in some other chronic disease, such as heart dis-

case or carcinoma.<sup>2</sup> If such points are given consideration, then the frequency of pulmonary tuberculosis in diabetic patients at autopsy appears to be from two to four times as great as it is in nondiabetic patients, and the incidence would be even greater if one selected from the autopsy series only those diabetics who are known to have had diabetes for a minimum of five years. The first clinical method of studying the incidence of tuberculosis is the use of consecutive roentgenograms. This method showed at the Deaconess Hospital during 1930 and 1931 that, in 1,659 diabetic patients, active pulmonary tuberculosis was present in 2.5 per cent, or probably five times as frequently as in nondiabetics of similar age distribution. In 1938, among 366 patients similarly studied, the incidence was 3.0 per cent. A test of the incidence of tuberculous infection by means of the Mantoux skin test in children showed that up to 1932 about 45 per cent of the diabetic

TABLE 1  
*Incidence of tuberculin reactions among diabetic children, 1937*

AGE	TOTAL CASES	NUMBER TUBERCULIN POSITIVE
<i>years</i>		
1-5	8	5
6-10	27	9
11-15	32	11
16-20	2	1
	69	26

children had positive tests in Boston, and that was the same as in Vienna. In 1937 the positives had fallen a little, namely to 37 per cent (Table 1). The curves of mortality rates from diabetes and tuberculosis continue to converge. In Massachusetts the rate for pulmonary tuberculosis for 1936 was 40.4 per 100,000 persons and for diabetes 31.7 per 100,000. The city of Boston mortality rate for diabetes in 1937 was the highest ever recorded, 32.2 per 100,000 persons, and the rate for pulmonary tuberculosis fell to 45.3 per 100,000. In Boston twice as many deaths occurred in diabetic females as in males. The former almost universal tuberculous infection of the community is diminishing.

<sup>2</sup> Personal communication. Mr. Herbert Marks notes that, in the Registration area of 1925, cancer deaths totalled 95,735, in 273 of which tuberculosis was reported present. The corresponding figures for diabetes were 18,810 with tuberculosis also reported in 537. Age, sex and differences in duration should be considered.

The great increase in diabetes is due largely to better diagnoses, better treatment and the increased longevity of the population, bringing more people into the diabetes age period. It is striking that the mortality from tuberculosis among diabetics shows no fall comparable with the falling rate among the general population, even though allowance is made for the increase in longevity of diabetics.

#### AETIOLOGICAL FACTORS

A history of contact with active cases in the family or friends was obtained in 129 of these 364 cases. We have no accurate data as to the sputum tests in possible contacts and, therefore, these histories are subject to correction. Occupations of the group were variable. Indoor, sedentary occupations were recorded in 80 per cent. Exposure to hard metal or rocky dust was rare in this group. Three out of 50 deaths among diabetic doctors were due to pulmonary tuberculosis, 6 graduate nurses in this group had tuberculosis, of whom one had worked in a tuberculosis hospital. In his consideration of the factors in the decline of tuberculosis, Wolff (11) emphasized the constitutional factor and the nutritional factor. In the diabetic group this factor of nutrition stands out preeminently. The age and sex distribution in tuberculosis among diabetics is atypical, in that a large diabetic group is of necessity largely made up of individuals past forty years of age. Only 10 per cent of all cases of diabetes begin in childhood and 60 per cent of them begin after the age of forty years. Therefore, if pulmonary tuberculosis tends to develop in diabetic patients after prolonged duration of diabetes, naturally the population of the diabetic group will be predominantly in middle and late life. It is not strange, therefore, that among our deaths children have been few. Among 1,063 diabetic children treated between August, 1922 and 1937, 101 deaths occurred. In the first five years of this period the children who died did not live long enough to acquire tuberculosis and actually of the 35 deaths during that five year period 91 per cent died from coma and the average duration of life of the child was only 2.7 years. During the next five years, among the 27 deaths, 2 were from tuberculosis. From 1932 to 1937 when the average duration of life was nine years and therefore the exposure to contact the tuberculosis was greater, among the 42 deaths there were 7 from tuberculosis, or a percentage of 17. Thus in the last fifteen years there have been 9 deaths from tuberculosis out of 101. Actually, the incidence of tuberculosis increases with the duration of diabetes and, in fact, of the 10 deaths

among children whose duration of diabetes was ten and fifteen years there were 4, or 40 per cent, due to tuberculosis (3)

Among 258 fatal cases, no deaths occurred in the first decade and only 5 in the second decade. Only about a quarter of the deaths occurred under the age of forty years. The unusual predominance of the male rate after the age of thirty in proportion of 3 to 1 is yielding to the greater frequency of diabetes in females. Actually 50 per cent of the deaths recently have been in females. Diabetic women, however, are much less likely to continue industrial employment and, therefore, are less exposed to tuberculous infection. Although tuberculosis is emphasized as the great danger in youth, in diabetic patients it is also a great danger of late life. Actually, if one takes into account the total number of persons living at different age levels and the threat to his associates caused by an open lesion in an older individual, tuberculosis is a greater menace in old age than in youth. Race plays little rôle in this group of patients. About 10 per cent in this series were Jews, and Jews form about 13 per cent of the larger series of diabetic patients studied by Doctor Joslin.

#### PATHOLOGY

Distinctive morphological features of tuberculosis in diabetic patients have been sought to explain its great frequency. Curiously enough, there are comparatively few autopsies performed upon tuberculous diabetic patients in which the details of the examination are sufficiently complete to make careful comparisons with nondiabetic tuberculosis. At the Deaconess Hospital we have had only 15 autopsies performed upon tuberculous diabetics, and we were only able to gather 126 autopsies performed upon tuberculous diabetics from various sources. Wiener and Kavee (4) added 48 autopsies of diabetics, comparing them with 48 nondiabetic cases. The types of tuberculous lesions found at autopsy in diabetes, although varied, show a striking predominance of the pulmonary form. The larynx and intestines have been involved but rarely, actually only 3 in 126 diabetic cases tabulated. Tuberculosis of the intestines is more common in the ulcerative type of tuberculosis than in the chronic fibrous type. Nevertheless, only 2 cases of tuberculous ulcer of the intestines were found in 92 autopsies of diabetics reported by Seegen in contrast with 50 per cent to 80 per cent of cases dying of tuberculosis reported by Brown and Sampson (5). The menin-

ges and brain were not involved in a single case of the 126 autopsies, but isolated cases are occasionally reported

*Pleurisy with adhesions* A striking feature was brought out by Wiener and Kavee They found that tough fibrous plural adhesions were twice as common in nondiabetic patients as in the diabetic This fact, while suggesting at first lack of the defensive response with fibrosis, also suggests an explanation of the clinical fact that in diabetic patients it is so often easy to use pneumothorax with excellent results Pleurisy does occur in all its forms in diabetics, but in our series of 364 cases onset of tuberculosis with pleurisy and effusion was notably rare

Healed tuberculosis may be found either as small healed foci in the lungs, or what is more important, numerous healed and healing processes in the lungs of patients who, nevertheless, have active pulmonary tuberculosis which causes death Unquestionably, in our series of autopsies pleural adhesions and small calcified foci were entirely disregarded A complete picture therefore of the extraordinary power of healing possessed by many diabetic patients, if they are given a good chance, is not available

*Caseation* Tuberculosis in diabetics has often been described as characterized by large extending areas of caseation Caseation, as a term applied to coagulation necrosis, occurs in the nondiabetic tuberculous as well Just as cheese is a mixture of coagulated protein and finely distributed fat, so in caseation there is coagulation of tissue protein associated with deposition of fat Again we are reminded of the disorders of the fat metabolism in the diabetic

It is true that acute generalized tuberculosis, such as occurs in childhood, is rare in diabetes Tuberculosis of the joint surfaces is uncommon If one compares the pathology of tuberculosis in the diabetic with that of the Negro, certain features are similar, such as the frequency of acute pneumonic lesions and extensive caseation The diabetic seems to have had normal resistance as judged by the number of calcified foci remaining from earlier infections, but in some manner loses his resistance after the onset of the diabetes

If we turn now to the distinctly biological aspect of the problem, we will consider first the tubercle bacillus itself Certainly in our own cases the ordinary acid-fast staining organism was found in the sputum in about the same proportion as in nondiabetics, so that we could not support the old statement often heard that the tubercle bacillus was difficult to find in the sputum of the diabetic The variations in form



and growth of the organism, which have been studied in recent years particularly by Petroff in this country and by other bacteriologists elsewhere, suggest that possibly in the diabetic patients differences in form of the organisms under slightly different cultural conditions might occur

A hypo-allergic state, especially following pneumococcal infection, has been stressed by Thiéry (1) and Labbé as explaining the explosive tuberculosis of diabetics

*Lipoid changes in diabetic tissues* One wonders whether the metabolic characteristics of the diabetic patients might have a bearing upon the growth and development of the organism in the diabetic lung No other organism has been so carefully studied as the tubercle bacillus The distinctive feature is the waxy substance, although protein and carbohydrate and fatty substances with mineral residue are present The lipids compose 10 to 40 per cent of the dry weight We can best refer the reader to the summary by Long of the more important chemical and metabolic features of the organism in relation to nutritional requirements of the tubercle bacillus, and to the recent study by Boissevain and Schultz (10) of a special fat-soluble growth promoting substance Its mineral requirements are simple It obtains its nitrogen from the amino group, its own proteolytic enzymes are weak, so that it does not grow well on whole protein However, ammonium salts and amino-acid amides are sufficient The protein metabolism is seriously disturbed in diabetics during serious acidosis, particularly during coma Great loss of weight and destruction of protein occur Occasionally in severely uncontrolled diabetic patients nitrogen excretion of 25 to 30 g occurs in twenty-four hours During acidosis values from 30 to 35 g have been reported Recurrent or mild persistent acidosis is naturally more common Glycerol appears to be the only alcohol acting as a source of carbon for the organism In the diabetic the disturbance of the fat metabolism must at times set free an unusually abundant amount of glycerol in the blood and tissue fluids Unfortunately, no analyses of the blood for glycerol were made during diabetic coma It has seemed to many students that in some way the cultural conditions favorable to the growth of the tubercles are linked with the fat metabolism

*Lipid content of diabetic lungs* One of the most characteristic features in the tissues of diabetic patients is the remarkable alteration of the fat content of certain organs The removal of fat from one tissue and its

deposit in another has been correlated with certain well recognized changes in the severity and intensity of the diabetes. Thus certain cases of diabetic coma, occurring particularly in emaciated patients of long duration, demonstrate a marked infiltration and increase in the fatty content of the liver. Under similar circumstances, especially if the patient is cachectic, an increase of blood lipids consisting of cholesterol, fatty acids and often free fat occurs, such that there may be a deposit in the spleen producing the characteristic fat-filled foam cells. Recent analyses of lipid content of livers removed at autopsy at the Deaconess Hospital by Miss Halliday and Miss H. Hunt have shown in 7 nondiabetics an average cholesterol content of 177 mg. in comparison with 417 mg. in 7 diabetics. The average phospholipid content for the same nondiabetic livers was 1,774 mg. whereas for the diabetic group the average value was 1,949 mg. per cent. Excessive lipid content of the liver and blood can be controlled by means of insulin so that a patient may lose the excessive fat within a few hours or days with proper treatment, the excessive fat being either metabolized or deposited in more normal tissue depots. A chronic type of fatty change is the excessive atherosclerosis found in diabetics characterized by a rich deposit of cholesterol and other fatty substances in the intima of the muscular arteries.

It has long been known that in degenerative conditions of the brain and central nervous system a decrease in the lipid content of the tissues may be found. Actually in diabetics, Jordan, Randall and Bloor (6) found that the lipid content of nerves, studied in amputated legs or at autopsy, was materially reduced in comparison to the normal. Although this change was often correlated with vascular disease, it did seem more definitely related to diabetic neuritis. It is clear, therefore, that alterations in lipid content in the tissues of diabetics can be correlated with clinical conditions. It becomes of considerable interest, therefore, to know whether or not the lipid content of lung tissue could be related in any way to the resistance of the diabetic lung to tuberculous infection. Analyses of lungs removed at autopsy at the Deaconess Hospital were carried out in Professor Bloor's laboratory. The method was to remove a section of lung tissue from the upper anterior portion of the lung where oedema and postmortem changes would be least important. The specimen was immediately placed in especially prepared solutions for chemical analysis. It must be admitted, however, that in the older group, including especially patients with coronary disease,

TABLE 2

*Lipid content of lung tissue in 26 diabetics and 2 nondiabetics*

PA- THOL- OXY NUM- BER	DIA- BETIC CASE NUM- BER	SEX	AGE AT DEATH years	DURA- TION OF DIA- BETES years	CAUSE OF DEATH	PATHOLOGY			LUNG LIPIDS, GRAMS PER 100 G WET TISSUE		
						Pancreas	Lungs	Miscellaneous	Phospholipid	Cholesterol	Ratio Phospholipid Cholesterol
25,531	*	F	57	12	Coronary thrombosis	grams 100			2 44	0 42	5 8
31,660	13356	M	61	17	Primary carcinoma, bronchus, metastases to liver, pancreas, spleen, etc	90	Carcinoma	General arteriosclerosis, moderate infarct, fatty liver Coronary arteriosclerosis	1 82	0 56	3 3
25,543	2021	F	52	14	Coronary thrombosis	50	Atelectasis both lower lobes	Aorta cholesterol clefts, numerous lipid-laden phagocytes, slight arteriosclerosis, cardiac infarction	1 71	0 34	5 0
24,559	12130	F	62	2	Cardiac infarction	90	Pulmonary embolism, healed pulmonary tuberculosis	Aorta focus of many large cholesterol clefts, fatty infiltration of liver	1 63	0 54	3 0
29,077	2903	M	75	15	Abscess of lung	90	Bronchiectasis	Aorta cholesterol clefts and foci of lipid filled phagocytes, lipid histiocytes of spleen	1 60	0 42	3 8
24,142	13150	F	50	4	Acute purulent pericarditis	No weight	Healed apical tuberculosis, pulmonary congestion	Slight fatty infiltration of liver	1 55	0 41	3 8
31,185	14756	F	23	2	Diabetic coma	60	Oedema, chronic fibroid tuberculosis, apex of left lung	General arteriosclerosis	1 50	0 38	3 9
24,502	15296	F	75	24	Cerebral thrombosis, acute pericarditis	130	Congestion	Aorta some cholesterol deposition, one cholesterol stone in the gall bladder	1 27	0 36	3 5

23,783	5793	M	64	14	Coronary thrombosis	140	Healed pulmonary tuberculosis	Aorta some cholesterol deposition in subintima layer with hyalinization in surrounding regions, fatty infiltration of liver	1 25 0 43	2 9
23,365	3194	F	62	12	Acute endocarditis	Atrophy	Healed pulmonary tuberculosis	Aorta some cholesterol clefts, rheumatic endocarditis (old), recent endocarditis and pericarditis, moderate arteriosclerosis	1 24 0 34	3 6
32,879	*	M	61	5	Cerebral haemorrhage	100	Passive congestion, bilateral hydrothorax	General arteriosclerosis	1 23 0 49	2 5
29,627	4247	M	69	14	Carcinoma of sigmoid	20	Slight, early bronchopneumonia	Aorta cholesterol deposition, fatty metamorphosis of liver, arteriosclerosis	1 12 0 43	2 9
28,150	11362	M	61	3	Cardiac decompensation	80	Atelectasis left lower lobe	Nephrosclerosis, generalized arteriosclerosis, coronary sclerosis	1 08 0 29	3 7
23,669	7465	F	56	10	Coronary heart disease	25	Hydrothorax, left	Marked arteriosclerosis, coronary sclerosis	1 02 0 28	3 9
32,880	14660	F	60	2	Carcinoma, vagina	Atrophy	Left, lower lobe congested	Fatty degeneration of liver	0 95 0 40	2 4
24,355	13213	F	82	19	Gangrene	120	Pulmonary oedema	Aorta few small cholesterol clefts, one cholesterol stone in gallbladder of mulberry type	0 93 0 23	4 0
31,750	2681	M	58	14	Cerebral thrombosis	80	Calcified primary tuberculosis	Severe cerebral arteriosclerosis	0 89 0 35	2 5
31,241	14056	F	71	1	Coronary sclerosis	120	Pulmonary congestion and oedema, bilateral hydrothorax	Myocardial infarction (old and recent), fatty metamorphosis of liver with central necrosis	0 89 0 35	2 5
28,899	14301	M	65	1	Coronary occlusion	90	Pulmonary emphysema, congestion, hydrothorax	Aorta large plaques, cholesterol crystals, congestion of liver and spleen	0 89 0 34	2 6
29,792	9479	F	46	13	Sepsis right thigh	80	Bilateral hydrothorax, healed tuberculosis, lymphadenitis	Fatty liver, central necrosis	0 88 0 42	2 1

Note Lipid values are expressed in milligrams per 100 grams of moist tissue

\* Patients of Dr F. Gorham Brigham, to whom we express appreciation

TABLE 2—Continued

PATHOLOGY	CAUSE OF DEATH	DURA TION OF DIA- BETES	AGE AT DEATH	SEX	DIA- BETIC CASE NUM- BER	PA- THOL- OGY NUM- BER	LIPIDS GRAMS PER 100 G. WET TISSUE		
							Phospholipid	Cholesterol	Ratio Phospholipid Cholesterol
Pancreas									
		years	years			grams size			
	Pentontus	10	34	M	14683	31,132	0.85	0.27	3.1
	Hypoglycaemia	6	27	F	12882	23,524	0.82	0.24	3.4
	Rupture of arterioscle- rotic aneurysm of aorta	7	76	M	8036	23,304	0.73	0.22	3.3
	Chronic tubular nephritis	5	49	M	*	30,116	0.69	0.24	2.9
	Pulmonary embolism, paroxysmal tachycardia	7	59	F	8362	28,553	0.67	0.43	1.6
	Coronary thrombosis	6	66	F	15099	32,578	0.63	0.33	1.9
						Non- diabet- ics			
	Pulmonary embolism		75	M	31,309	31,309	0.91	0.29	3.2
	Renal insufficiency Prostatic hypertrophy		71	M	23,686	23,686	0.89	0.31	2.9
Lungs									
	Hydrothorax Pulmonary oedema								
	Fatty liver, tubular nephritis Aorta, cholesterol clefts, cen- tral necrosis of liver Fatty liver, severe coronary sclerosis								
Miscellaneous									
	Carcinoma of prostate, marked arteriosclerosis Cholelithiasis								

terminal congestion of the lungs, especially due to heart failure, may have appreciably lowered the figures for lipid content, although definite efforts were made to avoid taking tissue in dependent portions of the lungs, and to avoid inflamed areas if such were present

Very few figures are available for lung tissue in any animal. In rats, the lungs contained about 2 per cent phospholipid and 0.45 per cent cholesterol, in beef lung, the phospholipid is 1.5 per cent and the cholesterol 0.22 per cent. In human lung (two years) the phospholipid is 1.69 per cent and the cholesterol 0.46 per cent. All these figures are upon the basis of moist weight. Fallon (12) found that the amount of phospholipid in the lungs of rabbits increased rapidly after intratracheal injection of quartz particles.

In table 2 are listed clinical data regarding 26 diabetic and 2 non-diabetic patients together with the values for phospholipid and cholesterol content of the lungs. Values are given in grams per hundred grams weight of wet tissue. The first 12 cases listed are those in whom the phospholipid value exceeded 1.10, arranged in descending order, 7 of the 12 were females. Only 1 (31,185) was under thirty years of age, 3 were between fifty and sixty years, 6 between sixty and seventy years, 2 were seventy-four years old. Two nondiabetic patients at the foot of table 2, aged seventy-one and seventy-five years, showed values for phospholipid of 0.94 and 0.89. It is striking that among these 12 cases only 3 were cases of short duration. The remainder had had diabetes from twelve to sixteen years. The 3 who had had diabetes a short time included a young woman (14756) who died in coma and who had healed tuberculosis at one apex, another woman (13150) who died of acute pericarditis with associated healed tuberculosis and fatty liver, and a woman (12130) who died of cardiac infarction and, in addition, healed or healing tuberculosis. Actually 5 out of the 12 patients showed evidence of healed or healing tuberculosis at an apex. One diabetic, case 25,531, a patient of Dr. F. G. Brigham, had a value of 2.44 mg. She died of coronary thrombosis and had a fatty liver. Fat-filled livers were noted in 4 cases and in 5 there was lipoidosis of the spleen. The remaining 14 diabetics of this series who did not have an increase in phospholipid content included a physician who had a calcified primary tuberculous focus in one lung, and a woman, forty-nine years of age, with diabetes of twelve years' duration, who showed a small focus of healed tuberculosis.

If we turn to the cholesterol figures, the 2 normal cases had cholesterol

concentrations of 0.29 and 0.31 per cent, whereas the diabetic cases ranged from 0.23 to the maximum of 0.54 per cent. Fifteen of the 26 diabetic patients had cholesterol values of 0.35 per cent or higher and in this group we find 6 of the patients with healed apical tuberculosis and again the almost constant marked arteriosclerosis and fatty liver.

Actually in this small group, the cases with higher lipid concentrations in lung tissue showed much more evidence of past tuberculous infection. Further study is clearly needed, since the majority of the cases showed lower lipid concentrations than normal.

The low phospholipid value is to be considered together with the low phosphorus content of diabetic cataracts, described by Carey and Hunt, Waite and Beetham (13). The frequency of the development of tuberculosis in diabetic patients who have true diabetic cataracts has been stressed by Himsworth (14). It may well be that the low phosphorus values are related to the carbohydrate metabolism in such a manner as to affect the resistance to tuberculosis.

#### CLINICAL

Cases of glycosuria, not proved to be true diabetes, have been excluded from this series of 364 patients. For a diagnosis of pulmonary tuberculosis, the persistent finding of fine râles at the apex, X-ray evidence or sputum containing tubercle bacilli were accepted. The outstanding clinical fact is the rarity of cases with minimal lesions. Actually, prior to the discovery of insulin, we have been unable to find any proved case of diabetes and tuberculosis in which the tuberculosis had been discovered in a minimal stage. In this series of 364 cases we have only 17 and one of these was discovered solely because that child had her lungs X-rayed every four months for four years until the first lesion about the size of a five-cent piece appeared. Now, five years later, after violating all rules, she has a bilateral process and has received bilateral pneumothorax.

Of the 7 cases discovered since 1932 and listed in table 3, in 3 (6532, 5692 and 5635) the diabetes began during childhood and X-ray examinations were made as a routine follow-up because 2 had had coma and the third had had an X-ray film with suggestive increase in markings some three years previously. Case 4935 developed spontaneous pneumothorax with the slightest of symptoms. The other three patients had X-ray examinations made during the course of a hospital stay, occasioned by infection of a toe in cases 15959 and 13200. The charac-

teristic features of these early lesions in the entire group of 17 minimal cases were (1) localization in the apex in 7 cases, (2) softness and lack of a sharp marginal definition of the shadow, (3) the fact that the process was below the clavicle and at the level of the hilum of the remaining ten

TABLE 3  
*Seven diabetic cases with minimal pulmonary lesions*

CASE NUMBER	SEX	AGE IN 1938	DURATION OF DIABETES	SIGNS AND SYMPTOMS AT TIME OF X RAY FILM	LOCATION OF LESION	LATER COURSE
3133	F	42	16	Cough, dyspnoea	2.5 cm area of density in left lung field, fourth anterior interspace	Living in January, 1937
4935	M	55	13	Spontaneous pneumothorax about 10/5/37, slight dull ache on left side of his chest	In sixth and seventh interspaces on right in region of former pneumothorax there is an area of increased density	Living in November, 1937
5635	F	25	11	Diarrhoea	1.5 cm area in the fifth interspace on the right	Living in July, 1937
5692	M	20	11	No signs	Third and fourth interspaces show area of increased density suggesting parenchymal involvement December, 1934	Living in May, 1937
6532	M	28	11	No signs	Area of opacity, fifth interspace posteriorly, outer half of chest May, 1937	Sanatorium, living in July, 1937
15959	F	70	9		Small area running outward from right hilum to periphery on level with seventh interspace posteriorly	Living in October, 1937
13200	F	67	7		Small area of density right lung level with seventh interspace posteriorly July, 1937	Living in April, 1937

All 7 of these recent cases are living in contrast with the first 10, of whom 5 are dead

*Case-finding by X-ray follow-up* If pulmonary tuberculosis is ever to be found in a reasonably early stage in diabetic patients, all coma cases must have reexaminations at stated intervals after recovery from coma and all cases with suspicious parenchymal changes or calcified trachobronchial lymph nodes should have a similar follow-up During 1937,



108 such chest X-ray films were taken. Of 87 who had previously had diabetic coma, 4 were classified as showing suspiciously increased markings in the parenchyma, 9 had tracheobronchial adenitis with calcification, 1 showed old healed tuberculosis, and 1 showed an incipient lesion. Among 21 cases in whom X-ray films were taken because of previous somewhat suspicious reports, 5 were still regarded as suspicious, 1 showed old healed tuberculosis, 1 showed an active but minimal lesion which has since cleared appreciably after nine months in a sanatorium.

In contrast to these minimal cases and the cases picked up by routine X-ray examination, 77 of the remainder of the series were discovered after hospital admission, as a group. They again demonstrate the startlingly advanced character of most pulmonary tuberculosis when discovered in diabetics only after symptoms have developed. Thus of these 77 cases, 27 are already dead, 15 of these died within six months of the discovery of tuberculosis. The only chance of discovering tuber-

TABLE 4  
*364 cases of combined tuberculosis and diabetes*

	AGES AT ONSET OF DIABETES								
	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+
Diabetes	6	32	46	70	77	85	39	9	
Tuberculosis	2	24	50	66	51	85	60	19	1

culosis in a diabetic person in a reasonably early stage is to insist upon repeated X-ray examinations of the chest.

*Clinical course* In table 4 are shown, for 364 cases, ages at onset by decades of both tuberculosis and diabetes. Actually, 83 per cent of this series developed tuberculosis following the onset of their diabetes. Nevertheless, it must be remembered that in the vast majority of these patients the primary infection was earlier in life. It is the reactivation and the development of adult type progressive pulmonary tuberculosis that concerns us. It is true in occasional cases that such adult type tuberculosis has been present before diabetes and had become quiescent until the diabetes began. It is also true that many prospective diabetics who develop tuberculosis early in life will die of it before reaching the age where the diabetes would have had its onset.

The clinical course of the tuberculosis was variable. The onset of tuberculosis in diabetes is no more insidious than in nondiabetics.

Symptoms and physical signs are no more rare in the diabetic with tuberculosis than in the nondiabetic, although errors are often made in ascribing symptoms to the diabetes rather than suspecting tuberculosis. The signs are usually there if we but look for them carefully enough and frequently enough. Case 8712 had a negative chest X-ray film in April, 1933. He returned to the hospital in October, 1933 with advanced pulmonary tuberculosis with cavitation and was dead within two months. A case with such rapid development and extension is the exception rather than the rule. In the majority of our cases the onset was insidious and perhaps could be best described as gripe-like. Occasional cases of pleurisy with effusion occurred and 18 per cent of the cases reported haemoptysis at some time, although this was rarely the initial symptom.

In the course of the diabetes a striking feature in the adult was rapid loss of weight during the months or years preceding the development of tuberculosis. In 219 cases the average loss of weight was 42 pounds and loss of weight in excess of 75 pounds occurred in 19 cases. Sixty cases, or almost 20 per cent, were known to have had diabetic coma. If we had reliable data for the entire series, it is likely that the incidence of severe acidosis, even though it did not reach the stage of full coma, was probably close to 50 per cent of the series. The degree and severity of the diabetes as judged by the glycosuria and carbohydrate tolerance do not permit one to say that one type of diabetes is more apt to develop tuberculosis than another. It is true that, as tuberculosis advances and emaciation comes on, oftentimes the diabetes nearly disappears, but such increases in tolerance are occasionally seen in association with other types of infection even of a septic character if they are chronic and of long duration. The important question in the course of the diabetes is largely the degree of control and the maintenance of proper nutrition. In one instance, case 7131, a nervous and overconscientious girl restricted her diet too greatly in order to keep sugar-free and undoubtedly hastened the development of tuberculosis by marked under-nutrition.

*Tuberculosis in juvenile and adolescent diabetics.* To the 17 cases of pulmonary tuberculosis developing in patients in whom diabetes began before the age of 20 1 years, reported in 1934, we can add 15 new cases developing since that time. In this group of 32 cases there are 18 whose diabetes began before their fifteenth birthday. The incidence, therefore, of pulmonary tuberculosis of the adult type developing in 1,126

children whose diabetes developed before the age of fifteen years is 1.6 per cent. If this is compared with the incidence in 140,000 school children studied by Pope (7), in whom the development of tuberculosis was 0.12 per cent, the frequency in our diabetic children is about 14 times as great.

In table 5 are listed 15 recent cases of whom 3 have already died. Six are males and 9 are females. After having diabetes an average of 7.1 years, it is to be noted that the duration of life after the discovery

TABLE 5

*Fifteen cases of pulmonary tuberculosis in juvenile and adolescent diabetics, 1932-1937*

CASE NUMBER	SEX	ONSET OF DIABETES		ONSET OF TUBERCULOSIS	INSULIN*	LIVING OR DEAD	DATE	FOLLOW UP		CAUSE OF DEATH
		Date	Age					Height	Weight	
					units			inches	pounds	
3332	M	1-23	17.4	2-37	32	L	3-37	65	139	
4261	F	11-23	9.0	6-33	6 + 30	L	4-38	64	119	
5181	F	7-25	20.0	1934	24 + 16	L	4-38	63	120	
5635	F	1-26	12.7	11-36	40	L	1938	64	129	
5692	M	11-26	9.1	12-34	42	L	5-38	61	95	
6532	M	9-26	17.2	5-37	37	L	7-38	66½	115	
7047	F	6-28	11.0	5-32	102	D	1-35	65	117	Tuberculosis
7131	F	5-28	15.4	2-35	30	L	3-38	63	133	
7538	F	9-26	16.0	1934	21	D	10-9-34	62	98	Pulmonary tuberculosis
8754	M	11-29	20.0	3-36	27	L	1938	69	110	
10020	F	3-31	15.5	5-37	30 + 64	L	5-38	66	120	
11600	M	11-20	18.5	1-33		L	5-38			
12171	M	12-32	13.2	2-36		L	1938			
12385	F	1-29	10.0	11-33	36	D	1-9-34	56	67	Pulmonary tuberculosis
12757	F	1-25	1.1	4-36	46	L	8-38	53	82	

\* *Italic figures indicate protamine insulin*

of tuberculosis in these 3 cases was only a matter of months. On the other hand, the duration of diabetes in the 12 cases still alive was 8.8 years on the average before tuberculosis was discovered. All cases received insulin, except 2, whose records in sanatoria we have not yet obtained.

Among 201 diabetic children studied at the Deaconess Hospital, 42 per cent of the first decade and 74 per cent in the second had calcified tracheobronchial lymph nodes. Tuberculosis developed most frequently among the least well controlled diabetics. A free diet even

with insulin encourages tuberculosis. Undoubtedly contact with an open case has been present, but the development of progressive tuberculosis in young diabetics is measurably influenced by the type of diabetic treatment carried out.

*Diet and tuberculosis* The object of treatment in tuberculous diabetics should not be dictated by a slavish regard for sugar-free urine and a normal blood sugar, if that attitude leads to the use of a diet too poor in carbohydrate or to undernutrition or to the use of too large doses of insulin which may provoke an overactivity of the counter-regulatory and opposing influences in the organs.

1 Glycogen impoverishment leads to acidosis, which may be of acute life-threatening type as in coma or in lesser degree to weakness and loss of vitality and resistance in the organs. It also leads to hypoglycaemia and serious insulin reactions.

2 Hypercholesterinaemia is to be avoided since it is favorable to the development of arteriosclerosis manifested in angina pectoris, apoplexy and gangrene.

3 On the other hand, in toxic tuberculous patients, a low value for cholesterol in the blood plasma may be accompanied by grave insulin reactions and may itself indicate an increased susceptibility to the hypoglycaemic effect of insulin.

Bertram (8) believes that haemorrhages are in no sense due to insulin but rather to a diet improperly balanced with regard to carbohydrate. He feels that the haemorrhages are far more likely due to overactivity of the opposing regulatory mechanisms, which leads to an outpouring of adrenalin, increased tonus in the peripheral vessels and an increase in the minute volume in the lungs and so to increase of blood pressure. Such haemorrhages occur in many other types of conditions as well as tuberculosis, indicating that the important thing is not tuberculosis but the susceptibility of the diabetic to vascular damage when the adrenalin response is too great. In general, then, the diet of a diabetic tuberculous patient should have from 150 to 200 g carbohydrate and from 70 to 130 g fat. Sample diet for use with tuberculous patients may be classified as follows, on the basis of a patient weighing 132 pounds.

	CARBO- HYDRATE	PROTEIN	FAT	CALORIES
	grams	grams	grams	
1 Standard diet	150	80	100	2,100
2 Surgical diet, before operation	200	75	70	1,730
day of operation	100	20-30	40-50	880
3 Diet to increase weight	250	87	120	2,436

In table 6 is summarized the treatment of 20 patients with diet and insulin, particularly protamine-zinc-insulin.<sup>1</sup> It is noted that in two instances the number of calories prescribed per kilogram body weight is less than 30. In each, the patient at the time was confined to bed for a considerable period of time because of the surgical treatment of an

TABLE 6  
*20 tuberculous diabetics treated with protamine-zinc-insulin*

CASE NUMBER	SEX	AGE IN DECEM BER 1937	DURATION		HOSPITAL DISCHARGE DIETS					WEIGHT	CALORIES PER KILOGRAM	INSULIN DOSES	
			Diabetes	Tubercu- losis	Date	Carbo- hydrate	Protein	Fat	Calories			RI*	PZI*
4261	F	23 0	14 0	4 4	9-20-36	159	71	90	1,730	117	32 7	6	30
4856	F	49 8	14 8	7 9	2-38	150	80	110	1,910				80 at 7 30 a m 30 zinc-insulin crystals
4935	M	55 1	13 1	0 6	10-37	152	79	101	1,825	116	34 6		28
5181	F	32 4	12 4	3 9	2-37	300	87	91	2,367	120	43 3	24	16 one hour before supper
6287	F	27 5	15 5	5 4	1-38	180	96	95	1,969	92	47	12	28
6532	M	28 5	11 2	0 6	5-37	161	86	104	1,924	114	37	10	30
10020	F	22 7	7 0	0 5	11-37	149	82	100	1,824	120	33 4	30	64
10491	F	73 2	6 2	3 9	7-37	142	71	103	1,779	88	44 4	4	40
11327	F	36 3	5 3	1 2	9-37	150	80	110	1,910	132	32	26	24
12496	M	72 1	5 1	5 1	1-37	135	65	90	1,770	105	31 4		8
13200	F	66 9	7 9	3 2	2-37	149	60	81	1,565	137	25 1		8
13709	F	52 4	8 4	27 4	5-37	140	73	92	1,680	98	36		24
13874	F	20 5	2 7	2 2	9-37	168	74	87	1,751	101	38 1	4	28
14288	F	59 4	14 7	0 1	11-37	141	57	84	1,548	123	27 6	12	30
14953	F	39 8	3 8	1 1	11-36	180	80	110	2,090	111	41 6		28
15083	F	65 4	2 9	1 3	12-36	171	77	100	1,892	123	32		30
15131	F	49 4	11 2	1 0	12-36	170	82	101	1,917	120	35 1		52
15442	M	69 6	0 6	24 7	6-37	147	76	92	1,720	147	25 7		10
15959	F	69 3	9 4	0 4	8-37	153	73	100	1,804	105	37		12
15976	F	48 6	0 5	0 3	9-37	153	73	92	1,720	98	38 6		10

\* RI = unmodified insulin, PZI = protamine-zinc-insulin

infected foot. Each of these 2 patients was free from fever and the tuberculosis more or less quiescent. Indeed, the diet for the entire group represents diets prescribed at the Deaconess Hospital where the patients were under control preparatory to their transfer to sanatoria. These diets should, therefore, be regarded from the point of view chiefly as adjustment to the diabetes rather than as diets intended for long

continued use in the management of the tuberculosis. The striking fact appears that the diabetic patient with tuberculosis does not require any great increase in the amount of insulin in relation to his diet and body weight as compared to the diabetic without tuberculosis.

*Protamine-zinc-insulin* The advantages of protamine-insulin in treating pulmonary tuberculosis are easily seen. In sanatorium practice it reduces the frequency of injections from two or three times a day to a single treatment before breakfast. Furthermore, the steady and long continued action of protamine-zinc-insulin makes it possible to have a ~~steady and constant formation of glucose and it reduces the de-~~ continued action of protamine-zinc-insulin makes it possible to have a of severe insulin reactions. The peculiar property of protamine-insulin which makes possible marked gain in weight is of fundamental importance. This property has been studied both in animals and in human beings and especially described by Sherrill (9). Nevertheless, it is still easy for tuberculous patients, and particularly the emaciated advanced patient, to develop spontaneous hypoglycaemia and therefore still easier to develop hypoglycaemia under insulin treatment. Case 11419, male, 48 years of age, came into the Deaconess Hospital having been taking from 5 to 10 units of insulin. He was sugar-free, had oedema, and, when we found that the fasting blood sugar was as low as 60 mg in the morning, insulin was omitted and his diet increased to 250 g of carbohydrate a day. In addition to that he was given carbohydrate at his bed-side and urged to eat frequently between meals. One morning at seven o'clock he was apparently dying but revived promptly with an intravenous injection of glucose solution. He developed spontaneous hypoglycaemia with a blood sugar of 0.2 per cent (20 mg) without any insulin whatever. Case 15976, age 48, onset of diabetes in May, 1937, was discovered to have advanced tuberculosis in September, 1937. At this time her weight had fallen from 160 to 90 pounds. In the hospital the urine cleared up rapidly. She left the hospital taking 10 units of protamine-insulin a day. At the sanatorium the insulin dose was increased for a time and then came a period when the urine was sugar-free for a week with only 20 units of insulin once a day. One morning at 6.30 she was noted to behave queerly, by eight o'clock her neck was stiff and she had double Babinski signs. A physician in attendance considered tuberculous meningitis, probably because the pulmonary tuberculosis was advancing generally. However, insulin was omitted and to everyone's surprise within a few hours her symptoms cleared up. She died within a month of pulmonary tuberculosis.

*Diabetic coma* In table 7 is summarized the treatment of diabetic coma in a school girl who had active and advanced pulmonary tuberculosis but who showed neither fever nor râles during coma. In the treatment of diabetic coma it is fundamental to give sufficient insulin to bring about such an improvement in the carbohydrate metabolism that the blood sugar falls and the carbon dioxide combining power of the blood rises. Second, to treat the intense dehydration and loss of base from body tissues by administration intravenously and subcutaneously of sufficient salt solution to restore body fluid and electrolytes. On

TABLE 7

*Treatment of diabetic coma and pulmonary tuberculosis—case 70-47, schoolgirl, age 16, May 10, 1934—died of tuberculosis in January, 1935*

	URINE		BLOOD		BLOOD PRES- SURE	INSULIN	SALT SOLUTION	BLOOD TRANSFUSION	CAFFEINE	ADRENALIN 1:1000	EPHEDRINE	GINGER ALE AND ORANGE JUICE	GLUCOSE
	Sugar	Diabetic acid	Sugar	Carbon dioxide combining power									
	per cent		mg	vol per cent		units		cc	g	cc	mg	cc	g
Admission	4.8	++++	1,050	4	70/?	100	1,000 cc iv 1,500 cc sc		0.45	1	50		
2 hours			700	7	88/?	200		100					
4 hours					70/?	200	500 cc iv 1,500 cc sc	400	2.00	1			
8 hours			410	6	96/22	100							
12 hours	Trace		130	10	100/60		600 cc iv					500	
16 hours	0	0	160	16								300	20
Totals in 16 hours						600	5,100 cc	400	3.45	2	50	800	20

admission, this girl was unconscious and the blood pressure was barely obtainable at 70, her eye balls were soft, she had vomited repeatedly and gastric lavage yielded tarry black stomach content. An immediate injection of 100 units of insulin was given even before we learned that the blood sugar was 1,050 mg per 100 cc. In the next eight hours she received a total of 600 units of insulin and by that time the blood sugar had fallen to 410 mg. She also received a total of 4,500 cc of salt solution as well as one blood transfusion because her blood pressure failed to rise. As we look back now, it is unlikely that the drugs (caffeine, ephedrine and adrenalin) given her had any considerable effect. The

value of the blood transfusion is also doubtful in view of later experience and would not now be employed

*Prognosis* The utterly hopeless prognosis given to the diabetic patient with tuberculosis before the use of insulin was based upon the fact that tuberculosis was always discovered in an advanced state. Tuberculosis discovered in an early stage was unknown. The remarkable efficiency of insulin and modern dietary treatment in preventing death from coma and maintaining good nutrition, as well as the use of surgical procedures, such as collapse therapy, have brought almost as spectacular improvement in the outlook for the tuberculous diabetic as has the use of insulin in childhood diabetes.

The hope, however, for the future lies chiefly in earlier diagnosis and this means more frequent use of X-ray for young diabetic patients who

TABLE 8

*Duration of diabetes and pulmonary tuberculosis in 258 fatal cases*

PERIOD	NUMBER OF CASES	DIABETES	TUBERCULOSIS	TOTAL DIABETIC DEATHS	PER CENT TUBERCULOSIS
		<i>years</i>	<i>years</i>		
1898-1914, August 7	19	5 4	2 7	342	5 6
1914, August 8-1922, August 7	47	5 2	3 0	805	5 8
1922, August 8-1930	87	6 2	3 1	1,278	6 8
1930-1938, July 29*	105	10 1	4 0	1,880	5 6

\* We are indebted for the tabulation of these data to the courtesy of Mr. Herbert Marks of the Statistical Bureau of the Metropolitan Life Insurance Company.

have positive tuberculin tests and examinations for older patients, especially those who have had diabetic coma, at stated intervals as a routine check-up. The favorable course of tuberculosis in youthful diabetics when discovered early is well illustrated in case 2179, a boy whose diabetes began in 1921 at the age of sixteen years and whose tuberculosis was moderately advanced in 1929. He was alive in 1937 and in good condition. Case 5413, a boy whose diabetes began in 1926 at the age of fifteen, developed tuberculosis with positive sputum in 1932. He is at work now after having spent more than a year in a state tuberculosis hospital.

Effects of insulin can be illustrated by the fact that fatal cases treated with insulin lived 8.9 years and those treated without insulin lived 5.9 years after the onset of diabetes. In 1937 we have 20 cases alive more than five years after the discovery of active pulmonary tuberculosis, the average being twelve years. Actually, the prognosis for tubercu-



losis in a diabetic patient may be better than in a nondiabetic. When tuberculosis has developed in a diabetic patient untreated with insulin, a dramatic improvement in nutrition as well as in the tuberculosis with proper insulin and dietary treatment results.

More significant data are obtained from a consideration of table 8 giving the duration of diabetes and pulmonary tuberculosis in 258 fatal cases. It is seen that in each period of treatment beginning in 1898 up to July 29, 1938 there has been a steady prolongation of life after the onset of diabetes so that the average duration of life has risen from 5.4 years to 10.1 years. The improvement in the duration of life after onset of tuberculosis is less striking in actual years but almost as great in terms of percentage. The increase from 2.7 years to 4.0 years represents an increase of 50 per cent. In the last two columns are given the figures which bear upon the chance of the average diabetic patient developing tuberculosis. It can be seen that there has been no great change although the decrease from 6.8 per cent to 5.6 per cent is a hopeful sign.

The prognosis for activity outside of the sanatorium is vastly improved. Diabetic patients make excellent subjects for pneumothorax and even for thoracoplasty, both of which methods of treatment have been in common use in our diabetic patients in the sanatoria to which they have gone. Again the success of these surgical forms of treatment should be greatly enhanced in the future by earlier diagnosis of the tuberculosis.

#### SUMMARY

1 Study of the various aetiological factors in 364 diabetic patients with pulmonary tuberculosis points to the disturbed nutrition of diabetes as next in importance to contact with an open case.

2 Pulmonary tuberculosis developed in juvenile diabetics, whose diabetes began at or before the age of twenty years, more than twelve times as frequently as among pupils in the Massachusetts grade and high schools.

3 Of 73 patients recovering from diabetic coma between February, 1929 and November, 1932, 13 have developed pulmonary tuberculosis within five years.

4 The incidence of pulmonary tuberculosis in adult diabetes does not show a decrease in rate corresponding with the general decrease in tuberculosis mortality in the community.

5 Pulmonary tuberculosis followed the onset of diabetes in 83 per cent of the cases.

6 In 126 autopsies upon diabetics with pulmonary tuberculosis, many healed foci, a tendency for the formation of tough, fibrous, pleural adhesions and a high frequency of caseating lesions with cavitation were outstanding features

7 Chemical analysis of diabetic lungs showed strikingly lower concentrations of phospholipid and lipid than in nondiabetic patients

8 The discovery of tuberculosis in the minimal stage is still rare but 7 new cases are reported

9 The advantages of protamine-zinc-insulin in the treatment of tuberculous diabetics is discussed and dietary data are given

10 Among 258 fatal cases the average duration of diabetes to death has increased from 5.4 years to 10.1 years and the duration of pulmonary tuberculosis from 2.7 years to 4.0 years

11 Diabetic patients make excellent subjects for pneumothorax and thoracoplasty. Prognosis for the diabetic patients with pulmonary tuberculosis has been greatly improved by the introduction of insulin and can be still further enhanced by greater emphasis upon early diagnosis. The routine examination of every diabetic's chest by means of X-ray is recommended

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## ORAL TUBERCULOSIS<sup>1</sup>

JAMES CLUTE BRYANT

Tuberculous infection of the oral cavity does not appear to be as common as was formerly supposed. Observation of patients at Glen Lake Sanatorium, Oak Terrace, Minnesota, over a period of eighteen years, has disclosed 17 cases which are reviewed herewith.

The ulcerous processes have in all instances been secondary to a pulmonary condition. In most cases there has been an extensive involvement of the chest. Frequently there has been associated tuberculous spine, kidney, enteritis and rectal fistula. Tuberculous oral lesions have been seen for the most part in patients with a poor prognosis or in far advanced terminal cases.

It was thought at one time that tuberculous oral lesions were incurable. Some few lesions have healed however, but in most instances only when the patient's general condition showed improvement.

A tuberculous lesion of the oral cavity, like one of the vocal cords, is a persistent and chronic ulceration. If the patient has little or no resistance the lesion progresses steadily in the soft tissues. In two cases there was definite bone involvement. The bone surrounding the roots of a few teeth was gradually eroded, loosening the teeth and necessitating their removal.

Tuberculous lesions of the oral cavity have certain essential characteristics peculiar to themselves. They may occur singly or multiply. The mouth lesions of tuberculosis are presumed to appear first as small yellowish nodules which break down and ulcerate. The developed ulcer is a very painful open sore, especially so when the tongue is involved. Acidulous, salty, sweet and spicy foods prove irritating to the exposed nerve endings of the raw ulcer.

In describing a typical oral lesion, visualize a circular or irregular denuded area with a typically punched-out appearance, a millimetre or more in depth, situated in the tongue substance or the soft tissues of the oral cavity. The peripheral edge overhangs the denuded area.

<sup>1</sup> From the Department of Oral Surgery, Glen Lake Sanatorium, Oak Terrace, Minnesota

slightly In reality the edge is being constantly undermined, increasing the size of the lesion The tissue immediately adjacent to and circumscribing the tuberculous lesions presents a raised, swollen and inflamed appearance This infiltrated area around the lesion is soft on palpation in contrast to the hard induration of cancer The lesion may or may not be fissured It will vary from a few millimetres in size to involvement of half the mandible and adjacent soft tissues A thin pseudomembrane or plaque protects slightly the underlying raw muscle, nerves, blood vessels and other tissue The lesion may vary from shades of light gray and dirty yellow to a gray violet The violaceous color is due to the congested and cyanotic blood vessels laid bare by the lesion The larger lesions of long standing are sometimes sprinkled with yellow granular tubercles Slightly oozing ends of blood vessels give additional variation in color and design These minute endings of eroded blood vessels give some lesions a speckled red or raspberry appearance

In large denuded inactive areas, such as the oral pharynx, the lesions present an obvious pseudomembrane The plaque in this location is usually grayish white These lesions are not as painful as those on the motile tongue Deep fissures sometimes form in tongue lesions which develop into finger-like protrusions, radiating out from the initial lesion When the patient's resistance is low the protrusions become wider and wider and later coalesce until a huge lesion, irregular in outline, presents itself

The findings of tubercle bacilli in smears from the lesions afford a positive diagnosis Biopsy of the ulcer will give the characteristic picture of a tuberculous lesion

Success in treatment of tuberculous oral lesions is almost always coincidental with the patient's faltering condition If his general condition is improving, success may be met with in the treatment of the ulcer Or if the active process of lung tissue destruction slows down, the oral lesions sometimes heal although the ultimate fate of the patient remains the same If he is on a rapid down-grade, the infection in like manner continues to grow and spread Patients have gone to post-mortem examination with the greater portion of the tongue and soft tissues of the oral pharynx involved In one exceptional instance, however, the patient's tongue lesion was completely healed at postmortem examination three months later The exciting and aggravating cause of the ulcer here appeared to be broken teeth of an old denture Follow-

ing construction of a new denture, the lesion completely healed. There was an unhealed tuberculous laryngitis.

In another instance the patient's small tongue lesions healed of their own accord despite a slow but insidious progression of his pulmonary tuberculosis.

To make a set rule as to the eventual outcome of a tuberculous involvement of the oral cavity would therefore be a fallacy. It is worthwhile to continue therapeutic endeavors despite the apparent hopelessness of the situation. The soothing effect on the patient's mind in knowing that everything possible is being done for him is certainly worth the time and effort involved.

Inasmuch as the patient with a tuberculous oral lesion is more frequently a terminal case and consequently too ill, weak and listless to use the simplest prophylactic measures, a terribly foul mouth presents itself. There are present excessive accumulations of hard calculus and soft food material with resulting inflamed gums. This foul condition of the mouth is favorable to and naturally tends to increase the progress of the lesion.

The tuberculous lesions occurred as follows: 9 of the tongue, 1 of the tongue and mandible, 2 of the hard palate, 1 of the hard and soft palate, 1 of the pharynx and soft palate, 1 of the soft palate, 1 of the maxilla and 1 of the mandible.

Two cases presented a history of lesions forming in tooth sockets developed before admission.

In approximately 11,366 extractions over an eighteen-year period on patients for the most part with an advanced stage of tuberculosis, no tuberculous ulcerations of the tooth sockets were noted.

In the consideration of this remarkable circumstance, one must be cognizant of the fact that as a rule only patients with a favorable prognosis are given the beneficial treatment resulting from the extraction or removal of oral foci of infection.

*J. H.*, case 1630, an auto salesman, age 41 years, entered Glen Lake Sanatorium on December 15, 1924 with a diagnosis of laryngeal tuberculosis and pulmonary tuberculosis moderately advanced. Physical examination revealed signs of infiltration down to the second rib and fourth vertebral spine on the right and to the first interspace and third vertebral spine on the left. The epiglottis and false cords were swollen and oedematous and there was an ulcerated area present in the epiglottic pharyngeal sulcus. The cords were not

visualized but approximated well on phonation. Apparently the entire pharynx was oedematous. The X-ray report was bilateral fibroid pulmonary tuberculosis with cavity formation right upper lobe. His blood picture showed mild secondary anaemia.

He presented X-ray evidence as well as symptomatic evidence of tuberculous enteritis. He entered with a draining maxillary sinus which followed the extraction of the upper first molar in October, 1924 previous to admission. Four attempts to suture and close the opening met with failure and the sinus continued to drain.

His discharge diagnosis on December 24, 1925 was laryngeal tuberculosis, quiescent, pulmonary tuberculosis, arrested, tuberculous enteritis, apparently quiescent. He was advised to continue home treatment and particularly not to overexercise.

The patient was readmitted December 27, 1927. The left maxillary sinus was discharging a thick pus ranging from yellow to greenish-white in color. Six months previous to entering the Sanatorium the patient had the lower left first molar extracted. A small sinus remained which later developed into an ulcer. At the time of the patient's readmission it was 6 x 4 x 1 mm in size. It was irregular in form with prominent edges which were undermined. The uneven granular floor of the ulcer was covered with a yellow pus. Pin points of blood were discernible. The ulcer was quite painful from contact with food material and the necessary work of mastication.

A biopsy taken in March showed definite tuberculosis. The laboratory report was as follows: Many well formed tubercles in submucosal tissue, some show caseous centres. There is an occasional tubercle in the mucosa. There is focal infiltration. The extravasated blood is probably traumatic.

The patient's general condition improved and, under daily treatment with lamp and mercurochrome, the ulcer had decreased to a little more than half size by June 5, 1928. The edges of the ulcer did not appear to be as markedly infiltrated and raised as they were previously and the surface had a better color with little secretion coming from its surface. There was only a small amount of pus from the region of the first molar above. An examination in December, 1928 showed the ulcer practically healed with the exception of a small area which had been the anterior portion of the ulcer. The presence of pus from the maxillary sinus could not be demonstrated. The patient's general condition was considered excellent and he was discharged March 20, 1929.

The patient was readmitted March 11, 1930 with a diagnosis of pulmonary tuberculosis, tuberculous ulceration of the left mandible, tuberculous ulceration about anus and tuberculous enteritis.

The left maxillary sinus was considered healed. The ulcer of the mandible was larger than at any previous time. The molars remaining had been

denuded and lost The bony alveolar process supporting the second bicuspid was practically all absorbed leaving it loose and requiring extraction The first bicuspid was also involved and later extracted Two years later it was necessary to extract the almost completely denuded cuspid The ulcer at this time, extended from the median line well back into the soft tissues anterior to the tonsil The cheek was partly involved as were the tissues under the tongue on that side The patient died April 14, 1932 At postmortem examination, the ulcer was seen to have involved more of the anterior teeth and the roof of the mouth showed whitish nodules

*E M*, case 4908, age 51 years, was admitted to Glen Lake Sanatorium on June 9, 1932 and died June 29, 1932 He had a diagnosis of extensive pulmonary tuberculosis, disseminated throughout both lungs and calcified hilum nodes on the left side The sputum was positive He had tuberculosis of the tongue and his prognosis was unfavorable

The patient noticed white elevations scattered over his tongue in November, 1931 These recurred constantly and in January, 1932 he consulted a physician At that time he was employed and felt well The physician treated the lesions locally until March 10, 1932 with no visible improvement At this time his three remaining upper molars were extracted On March 20 he consulted another physician At this time his tongue was furrowed but he suffered no systemic effects Vincent's infection was diagnosed and he was unsuccessfully treated with neosalvarsan He experienced loss of weight and physical weakness which prevented his working In May he went to the Mayo Clinic A biopsy of the lesion was done and a diagnosis of tuberculosis was made He entered Minneapolis General Hospital on May 20 and was transferred to Glen Lake Sanatorium June 9, 1932

The patient was in poor physical condition with atrophic muscles and pallid color, and he was dyspnoeic He was unable to speak above a whisper His tongue was markedly swollen and thickened so that it almost filled the mouth There were nodules and ulcerations chiefly involving the left side The lesions were covered with a dirty grayish exudate The tongue was very painful and there was marked tenderness to the slightest touch He died June 29, 1932

*P Z*, case 5100, a farmer, age 59, entered Glen Lake Sanatorium on October 23, 1934 with far advanced bilateral pulmonary tuberculosis with bilateral cavitation The sputum was positive for tubercle bacilli Two years previous to admission the patient had had a biopsy of the tongue made for a chronic ulceration of a year's standing, which had been diagnosed tuberculosis A diagnosis of pulmonary tuberculosis was also made at that time

The admission examination showed a marked depression on the left side

of the tongue about a half inch from the tip where the previous ulcer had been surgically removed. On the anterior surface of the tongue on the right side there was a new ulceration which was about one centimetre in diameter. The edges of the ulcer were irregular and its surface was covered with a membrane-like structure which was gray in color. The ulcer was quite painful and the tongue substance around the ulcer was inflamed and swollen. The patient was quite hoarse from the time he was admitted until his death. The soreness in his throat increased all the time and it became more and more difficult for him to swallow food or take liquid nourishment. The patient's lower teeth were sharp and abraded. He wore a full upper denture which was quite old and worn, some of the teeth being broken and sharp. This condition of his own lower teeth and those of the artificial upper tended to cut and irritate the tongue lesion. They might have been the initial cause. The abraded edges of the lower teeth were rounded and smoothed with stones and a new upper denture was constructed. Following this treatment, the tongue lesion gradually decreased in size and when the patient died two months later, it was completely healed.

The postmortem examination showed chronic pulmonary tuberculosis and tuberculosis of the larynx, spleen, kidney, epididymis, testicle, prostate and intestines.

*R. S.* case 825, a 34 year old barber, entered Glen Lake Sanatorium on August 3, 1921, with an advanced bilateral parenchymal tuberculosis. The sputum was positive for tubercle bacilli.

There was an ulcerated area on the inside of the lower lip extending from the right central incisor to the first bicuspid in width and from the free margin of the lip to the gum margin. The surface of the lesion was covered with tough, warty-like excrescences. There were two deep fissures in this area. There was quite a bit of infiltration about the area. There was a small superficial ulceration of more recent development below the lip margin, opposite the left central incisor. On the left side of the tongue opposite the first molar region, there was a prominence of the tongue where it bulged through the opening left by the missing tooth. On this prominence there was a small superficial tender ulceration about one-fourth inch in diameter. Biopsy examination showed tubercles.

The history of the tuberculous lesions was as follows. A year previous to admission, a sore spot was noticed on the left side of the tongue which was painful when eating. This area became firm, and then filled with pus which broke and an ulcer formed. Granulations formed on the bottom of the ulcer and it was healed ten months later, after five months it again became sore and ulcerated, remaining so ever since.

In October, 1920 a cold sore developed on his lower lip which healed. On



the edge of this area an ulcer developed the size of a dime which discharged pus continuously. Shortly after this, three small ulcers developed in the pharynx which were extremely painful on swallowing. The ulcers were treated with silver nitrate during the winter. In April, 1921 he learned he had pulmonary tuberculosis. During the spring and summer while curing, the ulcers were practically healed. In October, 1921, while curing at the State Sanatorium at Walker, Minnesota, the ulcers on lip and cheek again developed, ulcerating, spreading and discharging from then on. The patient left April 6, 1922 against advice and he died August 8, 1923.

In addition to these cases 13 other patients were observed. Their main oral lesions were distributed as follows: tongue 8, palate and uvula 1, soft palate 3, alveolar ridge 1. One of these patients was discharged as arrested, 2 are declining at the time of writing and the remaining 10 patients have died.

#### CONCLUSIONS

1 Tuberculous lesions of the oral cavity are comparatively rare, only 17 cases being detected in the oral examination of some 7,000 far advanced cases over a period of eighteen years.

2 Tuberculous tongue lesions frequently have a history of mechanical irritation from sharp edges of decayed and abraded teeth, broken silver fillings, gold inlays, crowns or broken artificial teeth. These sharp edges traumatize the tissue.

3 Constant irrigation and bathing of the oral tissues by the salivary and mucous secretions render the oral tissues highly resistant to tuberculous infection.

4 Tuberculosis of the oral cavity is a secondary manifestation of a far advanced pulmonary condition with an unfavorable prognosis.

5 Where the prognosis is favorable, tuberculous oral lesions are seldom formed in tooth sockets following extractions, despite the presence of heavily laden positive sputum.

# BILATERAL TUBERCULOUS PLEURISY WITH EFFUSION<sup>1</sup>

An Analysis of Fourteen Cases

GLORGL C WILSON

Bilateral pleurisy with effusion in tuberculous patients is generally little more serious than effusion on only one side, but occasionally it causes distressing and even alarming symptoms and the patient's life may depend on frequent aspiration of both pleural cavities. That such an alarming complication has received so little notice in the literature suggests its rarity.

Ameuille (1) in 1917 reported that tuberculosis of the serous cavities, and especially of the pleura, was strikingly frequent in soldiers of the French army. He said that multiple serous infections were most frequently seen in young patients, rarely in those over twenty-four years of age. The serous membranes were involved in 270 out of 2,600 tuberculous soldiers. Isolated pleuritis was the most frequent, but in an unstated number of cases the pericardium, peritoneum, meninges or synovial membranes were involved likewise or alone. He found that the lungs did not become involved often.

Als (2) first reported an instance of bilateral effusion in a pneumothorax patient. Fishberg (3) reported another a few months later and said that Forlanini in the treatment of hundreds of patients had never met with a case. Nor had Saugman. He also stated that Brauer and Spengler (4) had said there was no such case in the literature. Peters (5) in 1925 reported 3 cases and at that time could find 20 others in the literature. Peters thought that bilateral effusion indicated a bad prognosis. An occasional case of tuberculous polyserositis (6, 7) has been reported since. Howard and De Veer (8) have produced multiple serous effusions in tuberculous guinea pigs by repeated inoculations of small amounts of tuberculin.

A study of the patients with bilateral tuberculous pleurisy with effusion under observation in a sanatorium seems worth reporting. At Gaylord Farm Sanatorium from January 1, 1928 to January 1, 1938, 1,552 patients have been admitted with a diagnosis of tuberculosis.

<sup>1</sup> From The Gaylord Farm Sanatorium, Wallingford, Connecticut

Fourteen patients with proved or probable tuberculosis developed bilateral pleuritis with effusion. In this group 5 were under twenty-five years of age, 5 were in their thirties and 4 were forty or more years of age. Youth seems not to be a factor in the development of this complication.

Nine patients were males and 5 were females. Five of the group were under pneumothorax treatment and one of these developed effusion first on the contralateral side.

Ten patients had pulmonary tuberculosis, 7 with definite involvement of both lungs. Three of these had tuberculous laryngitis also, and 2 had intestinal tuberculosis. There was pericardial involvement in 3 and peritonitis with ascites in another. The patient with the most extensive tuberculosis died three months after admission. Another had pleuritis with effusion and pericarditis develop as complications of empyema and spontaneous pneumothorax from which he died six months later. A third, who also had diabetes mellitus as well as far advanced tuberculosis, died of an embolus in the pulmonary artery after a long period of strict bed-rest. A fourth patient with far advanced pulmonary tuberculosis and intestinal tuberculosis made an uneventful recovery from bilateral pleurisy with effusion and pericarditis with effusion, but died in another hospital five years later after an exacerbation of his pulmonary tuberculosis. A fifth patient with tuberculosis in both lungs, spinal caries and tuberculosis of the knee is still bedridden seven years after resorption of bilateral effusion. A sixth patient developed acute glomerular nephritis shortly after resorption of bilateral effusion and while under treatment for bilateral pulmonary tuberculosis. He was transferred to a general hospital and has not been heard from since his discharge from there with chronic nephritis. A diagnosis of pericarditis was made at the general hospital but this may have been a complication of nephritis and not tuberculous. Two patients are working and the remaining 3 are showing satisfactory improvement under treatment. In these 10 patients bilateral pleurisy with effusion seems to have been an indication of the extent of the disease and in all of them it seems to have been the result of direct extension to the pleurae of underlying pulmonary tuberculosis.

Four patients with bilateral pleuritis with effusion had no demonstrable pulmonary involvement. One of these also had an effusion into a knee joint from which tubercle bacilli were isolated. He has been working for seven years. Another of the 4 has a tuberculous kidney.

for which she is under treatment. A third developed iritis which was diagnosed as tuberculous. She was given frequent small doses of tuberculin subcutaneously before she developed bilateral pleuritis with a small effusion into each pleural cavity. Her family doctor also heard a pericardial friction rub at one time. Aspiration of pleural fluid was attempted without success. She had frequent unexplained blazes of fever. She was taken to another hospital where she died. A report has not been sent to us. The fourth patient in this group was the sixty-five year old housekeeper at the sanatorium. Shortly after the onset of bilateral pleuritis, she began having severe pains in most of her joints, together with swelling of the joints of the fingers and toes. The effusion into the pleural cavities was slight. Her recovery from the acute arthritis and pleuritis was uneventful and she has been working for seven years since in spite of her advanced age. She was not diagnosed as tuberculous but is included because she might be considered as belonging to the group of allergic polyserositis.

## SUMMARY

- 1 Fourteen patients with bilateral pleuritis with effusion are reported.
- 2 Most of these patients developed pleuritis as a complication of extensive pulmonary tuberculosis and by direct extension from underlying disease to the pleura.
- 3 Four patients with no demonstrable pulmonary tuberculosis are included in the group. Two of these had tuberculosis elsewhere from which tubercle bacilli were isolated. In the other two, the tuberculous aetiology is doubtful.

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## ERYTHROCYTE SEDIMENTATION<sup>1</sup> 2

### *Its Practical Value in the Management of Pulmonary Tuberculosis*

THOMAS DE CECIO AND BENJAMIN J ELWOOD

Within the past ten years, the erythrocyte sedimentation rate has been advanced to the rank of a valuable laboratory procedure to aid the clinician in better evaluating moot clinical problems. Particularly has the literature lauded the significance of this phenomenon in the field of tuberculosis. It is claimed that the sedimentation rate is not only a very sensitive index of activity in tuberculosis, but also reflects the clinical course of the process and yields significant prognostic data.

In putting into practice these observations, it was our frequent experience that results did not conform accurately with the findings of others. This study was therefore undertaken to determine whether the sedimentation rate offers any added information which cannot be gained clinically or gives further assurance to the clinical impression. A total of 825 consecutive admissions were studied. Of these, the initial rates were analyzed in all, while in 338 detailed analysis of the serial rates was made. The latter group had one determination on admission, routinely once a month while in the hospital and in the Out Patient Department, at the time of any clinical complication or anatomical change confirmed by X-ray examination and on discharge. The method employed was that described by Cutler (1), the technique of which is well known.

Throughout the entire study the evaluations as to type of lesion, activity, course and prognosis were based predominantly on changes revealed by X-ray examination, the clinical findings serving only to corroborate the impression thus gained.

#### EVALUATION OF ACTIVITY

The impression is prevalent that the sedimentation rate is a highly accurate index of activity in cases of pulmonary tuberculosis. In fact,

<sup>1</sup> Read before the Clinical Section of the New Jersey State Tuberculosis League, January 5, 1938.

<sup>2</sup> From the Hudson County Tuberculosis Hospital, Dr. B. S. Pollak, Medical Director, Jersey City, New Jersey.

the statement is made in the literature (2) that "a normal sedimentation test was never obtained in an individual unless he was healthy or the disease which he was harboring was of such nature that little or no destruction of tissue was taking place at the time the test was performed, —certainly not enough to disturb the natural stability of the blood " There is a formidable number of authors (Masten (3), Siltzbach (4), Kaminsky and Davidson (5), Friedman (6), Morriss (7), Levinson (8), Briskman (9), Volk (10), Cass and Sutermeister (11), Banyai and Anderson (12)) who are more or less in conformity with this concept. There are others (Luzzatto-Fegiz (13), Sticotti (14), Bochall (15)), whose writings antedate many of the contributors mentioned above, who do not hold the test in so high a regard as an indicator of activity. Cutler's figures taken as representative of the former group, reveal that 87 per cent of clinically active cases have an elevated rate and that 97 per cent

TABLE 1  
*Correlation of initial sedimentation rate and activity*

	NORMAL RATE	ELEVATED RATE	TOTALS
Active	138	530	668 (79% elevated)
Inactive	86	71	157 (55% normal)
Totals	224 (61% active)	601 (88% active)	825

of inactive cases present a normal rate. Our work (table 1) substantiates these findings in part, in that 79 per cent of the active cases presented an elevated rate but only 55 per cent of the inactive cases showed a normal rate. These figures are not at too great a variance with those of Cutler, Masten, Siltzbach, etc. But when one considers further that, out of 224 admissions with normal rates, 61 per cent presented active lesions, the significance of the sedimentation rate in the determination of activity immediately diminishes markedly.

Considering activity based on the sedimentation rate in comparison with anatomical activity alone (substantiated by subsequent course), it was found that exudative lesions were associated with an elevated rate in 73 per cent of the cases and that productive lesions were associated with an elevated rate in 77 per cent of the cases. These figures are in accord with the view expressed by Bochall (15) that a differentiation between exudative and productive tuberculosis on the basis of the sedi-

mentation rate is not possible. Thus, the estimation of activity by determining the initial sedimentation rate is inconclusive.

#### COURSE OF DISEASE AND SEDIMENTATION RATE

Again the literature abounds with the writings of observers such as Cutler (16), Cass and Sutermeister (11), Spector and Muether (17), Friedman (6), Levinson (8), who feel that the sedimentation rate reflects accurately the course of the disease. On the other hand there are those, such as Voss (18), Sticotti (14), who, though concurring in the view just described, are wary of its accuracy.

In order to study this phase of the subject, the course of the disease was considered as "regressive," "mutative,"<sup>3</sup> "progressive," or "unchanged." These are not single observations but represent the trend of pathological change.

TABLE 2

*Correlation of the anatomical course of 338 cases and their serial sedimentation rates*

	TYPICAL	SOME SIGNIFICANCE	NO SIGNIFICANCE	TOTALS
Regressive	70	50	24	144
Mutative	39	35	5	79
Progressive	36	23	6	65
Unchanged	36	13	1	50
Totals	181(55%)	121(34%)	36(11%)	338

In 338 cases so studied (table 2) with serial rates it was found that in only 55 per cent did the sedimentation rate reflect the anatomical changes. Certainly, a clinical adjunct which is only 55 per cent accurate is not of great practical importance nor does it deserve, in our clinical armamentarium, so highly vaunted a place as the literature leads us to believe.

#### PROGNOSIS AND SEDIMENTATION RATE

The most interesting phase of this work was the comparison of the prognosis based on the sedimentation rate as against the clinical impression. In dealing with its prognostic significance in tuberculosis, the literature is rather extensive and one notes a fair diversity of opinion. There are those (Westergren (19), Siltzbach (4), Friedman (6), Roche

<sup>3</sup> "Mutative" refers to that characteristic of a lesion which for the period of observation demonstrated progression and regression either alternately or concurrently.

(20), Davies (21)) who highly praise its prognostic value, some even placing it above the clinical evaluation of a case, others (Frimodt-Moller and Barton (22), Heaf (23), Weichsel (24)) though agreeing that it is of some value are not wholly convinced and still others (Houghton (25), Beaumont and Dodds (26)) attach very little importance to the test prognostically

For comparative study a group of 182 patients, who were clinically and anatomically stable for at least three to six months before discharge, was analyzed. They divided themselves on leaving the hospital into two subgroups, those with elevated rates and those with normal rates. The study was continued without interruption in the Out Patient Department for a period varying from six months to five years (80 per cent for one year or more)

TABLE 3

*Analysis of sedimentation rates of discharged cases observed from six months to five years*

ELEVATED RATE ON DISCHARGE				NORMAL RATE ON DISCHARGE			
Reactivated		Unchanged		Reactivated		Unchanged	
After Rate Normal	While Rate Still Elevated	Rate Dropped to Normal	Rate Still Elevated	While Rate Normal	Rate Elevated Before or After	Rate Normal	Rate Became Elevated
3	17	39	69	7	6	39	2
20(16%)		108(84%)		13(24%)		41(76%)	
128				54			

It is interesting to note that of those discharged with an elevated rate (128), 108, or 84 per cent, remained well for six months to five years and that 50 per cent were still elevated after one to five years' observation. Of the 20 (16 per cent) that reactivated, 17 did so while the rate was still elevated. Of the group discharged with normal rates (54), 41, or 76 per cent, remained well over a period of one to five years, while 13 (24 per cent) reactivated during the period of observation. Seven of the 13 reactivated while the rate remained normal. Certainly, the group with elevated rates on discharge fared just as well as the one with normal rates (table 3)

Thus prognostically, the impression gained from a meticulous clinical and X-ray evaluation was by far more practical and more accurate than that deduced from the sedimentation rate, for out of a total of 182 cases eligible for discharge on a clinical and X-ray basis only 54 would have



been eligible on the basis of the sedimentation rate, with just as much chance for relapse as those with elevated rates

#### DISCUSSION

Realizing that, despite the findings presented, the sedimentation rate, perhaps in a modified form, might still reveal valuable information, accessory studies were undertaken. The first factor to be considered was that of the rôle of anaemia. The observations of Friedman (6) would indicate that correction for anaemia is essential, whereas Siltzbach (4) showed that in the majority of instances anaemia played an insignificant part. It was our impression that if corrections were made less conformity than already noted would be obtained. The more recent work of Cutler (27) substantiates our impression and proves conclusively that correction more often than not leads to erroneous results.

The second point considered was the actual curve or graph. Eliminating the phase of cell packing, and considering only the phase of cell aggregation and precipitation, no greater conformity or significance could be discerned, a fact which might well have been anticipated since the latter two phases are reflected in the sedimentation index. An attempt was even made at evaluation of the rate of change of sedimentation per five minute periods but no significant results were obtained.

It is important to note at this point the work of Patterson (28), who found a significantly low sedimentation index (1 to 7, average 3.5) for normal individuals. His findings lead one to feel that the accepted normal indices are too high. Patterson showed that, in 41 release cases with active tuberculosis, the average index was 8.1 and that in another group comprised of 65 active cases with multiple determinations the average index was 9.5. Perhaps a reconsideration of the normal standards is in order?

#### SUMMARY AND CONCLUSIONS

The study of the sedimentation rate with a view to establishing its practical value in the management of tuberculosis of the lungs reveals that

1. In the initial study of a case, the occurrence of an elevated rate indicates in a considerable majority of instances the presence of an active lesion. However, the presence of a normal rate does not exclude an active lesion.

2. In the correlation of serial rates with definite pathological trends,

the case percentage (55 per cent) of compliance of the rates with the anatomical course is not of sufficient significance to be of practical value.

3. No greater percentage of relapse or reactivation occurred in the group discharged with elevated rates than in the one with normal rates. And furthermore a considerable majority of those patients with sustained elevation of the sedimentation rate have remained well from one to five years.

4. The information obtained from the clinico-pathological study not only reveals all but more information than can be gleaned from sedimentation rates alone and with a greater degree of accuracy.

Thus the use of the sedimentation rate in the management of pulmonary tuberculosis as a criterion of activity, course and prognosis is not of sufficient clinical value to be essential in the care of the tuberculous.

Deep appreciation is herewith expressed to Dr. B. S. Pollak whose indulgence and encouragement made possible this work and to Dr. B. P. Potter whose stimulus and guidance played an inestimable rôle in the actual studies.

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# THE EPIDEMIOLOGICAL ASPECTS OF THE NEGATIVE TUBERCULIN REACTION<sup>1</sup>

M PARETZKY

The problem of the significance of primary infection in the immunology of tuberculosis has retained its interest up to the present time. The divergence of opinion among the investigators of the subject has added interest to this problem. As this problem can be satisfactorily solved only on the basis of facts, we feel that presentation of some material accumulated by us from observations on cases seen in the Chest Clinics of the Los Angeles County Health Department would be of some interest. It is our opinion that, in view of the fact that different negative reactors possess different immunity to tuberculosis, they should be accordingly divided into several different groups. In this paper we have divided them into four groups.

- 1 Persistently negative reactors possessing high specific immunity
- 2 Reactors previously sensitive to tuberculin, with a subsequent complete desensitization
- 3 Negative reactors with low immunity
- 4 Negative reactors subsequently becoming positive without developing the disease

In all studied cases the intracutaneous tuberculin (Mantoux) test was used.

## GROUP 1    PERSISTENTLY NEGATIVE REACTORS POSSESSING HIGH SPECIFIC IMMUNITY

The existence of reactors of this type has been known since the early days of tuberculin testing. It must be borne in mind that some of the persistently negative reactors possibly are desensitized formerly positive reactors with the positive phase of the tuberculin record remaining undiscovered due to the late initial tuberculin testing. However, beyond doubt, many persistently negative reactors never were tuberculin sensitive. As an illustration we wish to cite the following case.

<sup>1</sup> From the Chest Division of the Los Angeles County Health Department, Los Angeles, California.

*Case 1:* A little Mexican girl had a series of negative tuberculin reactions. She was first tested with a dose of 0.1 mg. at the age of nine months. During a period of four years, 9 applications of Old Tuberculin, including the doses of 1.0 and 10.0 mg., were done. During this period of time she was exposed to two relatives with active pulmonary tuberculosis. A third relative, formerly an arrested case, had broken down with active tuberculosis and had to be institutionalized. Due to the early age at which the initial negative tuberculin test was observed, it is certain that this child could not possibly have burned out her allergy if such had previously existed. It is also certain that she possessed an immunity of a remarkably high potency.

Obviously this is the most desirable type of "contacts" with immunity functioning at highest level possible, sufficient to protect not only from the disease, but from the implantation of infection as well. Therefore, negative reactors of this type warrant a detailed study. We have made observations on 90 patients of this type, all of whom were negative to all doses of tuberculin applied, including in each instance the dose of 10.0 mg. In many cases the dose of 10.0 mg. was repeatedly applied.

There were 52 females and 38 males among this group, or 57.7 and 42.2 per cent respectively. The age distribution was: up to 4 years, 23, or 25.5 per cent; 5 to 9 years, 30, or 33.3 per cent; 10 to 14 years, 24, or 26.6 per cent; 15 to 19 years, 8, or 8.8 per cent; 19 years and older, 5, or 5.5 per cent. The 90 reactors belonged to 46 families. The distribution per family was: one to a family in 25 families; 2 to a family in 9 families; 3 to a family in 7 families; 4 to a family in 3 families; 5 to a family, and 9 to a family in one family each. The average was approximately 2 cases to a family. This makes it suggestive that the factor of hereditary immunity has played an important part in the phenomenon studied.

Of course, all these 90 patients were diagnosed as nontuberculous on initial examination. On follow-up, 84, or 93.3 per cent, remained tuberculin-negative; 4, or 4.4 per cent, became positive reactors with negative clinical and roentgenological findings. Of these, one belonged to a family with a total of 5 negative reactors, 4 of which remained tuberculin-negative. This case was considered as indicative of the fact, frequently observed by us, that the evolution of the tuberculin record in cases of this type is often influenced by individual changes in the level of immunity. Three of the cases that eventually acquired tuberculoallergy belonged to families with one negative reactor in each. Two patients of this group, or 2.2 per cent, developed tuberculosis of the childhood

type, one soon became arrested. These 2 patients were members of the same family. We feel that a brief report of this family will be of interest.

*Case 2.* These 2 patients, Mexican girls, born in 1924 and in 1933 respectively, had an uninterrupted negative tuberculin record from January, 1935 to July, 1936. Four different tuberculin tests were made in the older girl during this period of time and six in the younger one. One dose of 10.0 mg. of Old Tuberculin was used in each case. At that time they were exposed to the mother who was diagnosed in December, 1934 as having active minimal pulmonary tuberculosis, and was pronounced arrested in August, 1936. A sister of these girls with moderately advanced pulmonary tuberculosis was placed in a sanatorium. She left it without permission in May, 1936, returned home and stayed there till June 8, 1936, on which date she returned to the sanatorium under compulsion. She died a few months later. As stated before, the two girls remained tuberculin-negative as late as July, 1936, a dose of 1.0 mg. of Old Tuberculin was applied to each of them at that time. In November, 1936 the girls had positive reactions to 0.1 mg. of Old Tuberculin. X-ray films taken then showed that the older of these girls had developed calcified tracheobronchial tuberculosis, and the younger hilar and parenchymal active tuberculosis of the childhood type. A follow-up film taken of the second case in May, 1937 showed only a slight decrease of the hilar shadows in both lungs.

The circumstances under which these two girls developed clinical tuberculosis are of interest. Some conclusions can perhaps be deduced from these cases. One is that negative reactors of this type, as a rule, endowed with high immunity, are liable to succumb to infection if a sudden increase of the dosage of infection to which they are exposed takes place. In other words, immunity even of the highest type is only relative and apparently limited to a certain dosage of infection and does not function beyond this limit.

Another conclusion confirming an old observation is that, in order to function efficiently, immunity apparently requires a more or less frequently repeating impact of infection of a certain potency. When this impact ceases or diminishes in its potency, immunity is likely to decline. Indeed, in the cited cases, both girls were tuberculin-negative though exposed to infection derived from two spreaders, their mother and sister. Later the mother became arrested and the sister was hospitalized. The dosage of infection to which the girls were subjected had decreased and perhaps even had come down to zero. Consequently, the girls appar-

ently lost a great deal of the previously existing immunity and, when their sister returned home for a few weeks only, they, being suddenly reexposed to a potent infection, developed tuberculosis.

As it was stated before, 81 or 93.3 per cent, of the observed negative reactors of this group remained tuberculin-negative.

In view of the evidently persistently high immunity of these 90 individuals it would be of interest to analyze the features of infection to which they were exposed. Among them there were exposed to one case of active tracheobronchial tuberculosis and one case of minimal pulmonary tuberculosis arrested at the same time, 1 case, or 1.1 per cent, to minimal pulmonary tuberculosis arrested 5 cases, or 5.6 per cent, to minimal pulmonary tuberculosis active, 22 cases, or 24.4 per cent, to moderately advanced pulmonary tuberculosis active, 29 cases, or 32.2 per cent, to far advanced pulmonary tuberculosis, 12 cases, or 13.3 per cent, to more than one case of active pulmonary tuberculosis at the same time 20, or 22.2 per cent, to silicotuberculosis, 1 case, or 1.1 per cent. Altogether 61 negative reactors, or 67.8 per cent, were exposed to advanced cases of pulmonary tuberculosis.

The progress of the infecting cases could serve as another criterion of the degree of infection to which the 90 negative reactors were subjected. Of the 57 infecting cases, 1, or 1.8 per cent, was eventually cured, 11, or 19.3 per cent became arrested, 14, or 23.6 per cent, improved, 15, or 26.3 per cent, remained stationary, 8, or 14.0 per cent, became worse, 6, or 11.6 per cent, died. In 2 cases, or 3.5 per cent, there was no information as to the progress. It is of interest that in a fourth of the infecting cases there was a definitely unfavorable progress of the disease.

Eighteen, or 20 per cent, of the persistently negative reactors were exposed to 9 infecting cases with sputum occasionally positive for acid-fast bacilli. It is worth mentioning that 9 of these reactors belonged to two families, 4 and 5 respectively to a family. Again 18, or 20 per cent, of the persistently negative reactors were exposed to 7 infecting cases with sputum constantly positive for acid-fast bacilli, 13 of these reactors belonged to two families, 4 and 9 respectively to a family. Altogether, 36, or 40 per cent, of the total were exposed to cases with positive sputum, or, in other words, to considerable doses of infection.

The nature of exposure was constant and prolonged in 50 negative reactors, or, in 55.6 per cent of the total, constant but short in 10 cases, or in 11.1 per cent, almost constant in 10 cases, or in 11.1 per cent, with considerable interruptions in 16 cases, or in 17.8 per cent, occasionally in

3 cases, or in 3.3 per cent, there was no information in 1 case, or in 1.1 per cent

The analysis of different phases of infection to which the 90 persistently negative reactors were exposed has brought out the significant fact that on the whole we have dealt with a group exposed to infection of considerable dosage and virulence

We feel that, for the sake of comparison, other "contacts," which belonged to the same families as the reported 90 individuals, ought to be studied. Of the 46 families under consideration, in 4 families there were no other "contacts," in 42 families there were 135 other "contacts," of them 85 were positive tuberculin reactors on initial testing, 50 were negative tuberculin reactors

The initial diagnosis of the positive reactors was as follows: tuberculosis of childhood type arrested, 9, tracheobronchial tuberculosis active, which later became arrested, 1, minimal pulmonary tuberculosis arrested, 1, nontuberculous, 68. On reexaminations there were discovered among the positive nontuberculous reactors 2 cases with slight calcification, 2 others developed active childhood type tuberculosis, both of these cases became soon arrested

The 50 negative tuberculin reactors mentioned above were not tested with high doses of Old Tuberculin. The dose of 10.0 mg. was not applied to any of the 50 individuals. Therefore it was deemed proper not to include them in the group of the 90 persistently negative reactors to all of whom the dose of 10.0 mg. of Old Tuberculin was applied, but to study them as a separate group

On retesting, 20 of them had become positive reactors and one of these had developed slight pulmonary calcified lesions. Thirty negative reactors of this group have not changed their negative response to tuberculin

#### GROUP 2 REACTORS PREVIOUSLY SENSITIVE TO TUBERCULIN WITH A SUBSEQUENT COMPLETE DESENSITIZATION

Some tuberculin-positive individuals manifest a tendency to a more or less complete spontaneous desensitization. We have reported (1) observations on 80 cases of this type, with a definitely established previous tuberculin record, which have in the course of time lost their specific hypersensitiveness to the extent that they failed to react to 10.0 mg. of Old Tuberculin. At present we shall limit ourselves to a brief reiteration of some of the immunological observations related to the subject of this paper

Many of the 80 cases were exposed to considerable doses of repeated reinfection, the virulence of which was confirmed by the relatively frequent occurrence of positive sputum and of eventual death among the spreaders of infection. Some new cases of active tuberculosis have developed in the families exposed to the same infecting cases. Under these circumstances the fact of disappearance of hypersensitiveness in these 80 subjects, combined with the clinically observed complete freedom from disease among 80 per cent of these cases, testifies to the high level of immunity in these subjects. While in the majority of the studied cases of this group this phenomenon was purely an individual one, being limited to one member of the family only, there was ample evidence that in some other instances hereditary immunity was a powerful factor of desensitization. A tendency to reappearance of specific hypersensitiveness was observed in some of these cases. Nevertheless, desensitization has remained unimpaired in two-thirds of these cases at the time they were first reported by us. It is self-evident that one cannot speak of this group as of one consisting of genuine and persistent negative reactors as all of them had a previous positive tuberculin record. One cannot contend that the comparatively high level of immunity observed in these cases was due primarily to their total freedom from infection in the later period of their tuberculin record, as manifested by a negative reaction to 10.0 mg. of Old Tuberculin. Just the reverse, we can visualize how primary infection was implanted in these subjects and how the mechanism of inherent individual immunity which was not sufficiently potent to prevent this implantation was brought into powerful action by this infection, and, at the following stage of this struggle against infection, it was successful in achieving a gradual but complete elimination of infection. In other words, there is ground to believe that the high level of immunity in these cases was originally due to the positive phase of their tuberculin record. One wonders how many cases that are persistently tuberculin-negative over a long period of time are actually of this type, the positive phase of their tuberculin record remaining unknown because they were first tested after their specific hypersensitiveness had already completely disappeared.

Additional observations were made by us after these cases were first reported. We feel that some of them are of sufficient immunological interest to warrant a further report.

*Case 3* A Mexican girl, born in 1927, had an initial positive tuberculin reaction with a negative X-ray film in 1931 and a series of negative reactions to



different doses of Old Tuberculin including several of 10.0 mg, from 1933 to 1936. She was exposed to the mother, who had minimal pulmonary tuberculosis with a practically stationary course of disease from 1931 to 1936. By the end of 1936 the mother took a sudden and rapid change for the worse. She was placed in a sanatorium and died there in March, 1937. In April, 1937 the daughter had a three-plus reaction to 0.1 mg of Old Tuberculin and the X-ray film showed evidence of active tracheobronchial tuberculosis.

*Case 4* Two white twin sisters, born in 1929, had an identical tuberculin record from 1930 to 1936, starting with a negative tuberculin reaction in 1930. In 1933 they both had positive reactions to 0.01 mg of Old Tuberculin. In 1934 they had again negative reactions to 0.1 mg of Old Tuberculin. During the following two years they had a series of negative reactions to different doses of Old Tuberculin including several doses of 10.0 mg. In May, 1936 one of the twins had an attack of measles. Tested again August, 1936 she had a three-plus reaction to 0.1 mg of Old Tuberculin. The X-ray film revealed a large irregular area of increased density at the left hilum extending into the midlung field which was diagnosed as primary pulmonary and tracheobronchial tuberculosis. The other twin sister escaped the attack of measles and in August, 1936 had remained negative to a dose of 1.0 mg of Old Tuberculin. The twins were intermittently exposed for a number of years to their father who had far advanced pulmonary tuberculosis with sputum positive for acid-fast bacilli. During the spring and summer of 1936 the father stayed at home.

These two cases are of interest inasmuch as they stress the epidemiological importance of two major factors. In the first case the factor responsible for the defeat of immunity which demonstrated its high efficiency over a period of years was exogenous infection. Immunity was successful in checking and subsequently completely eliminating the primary infection to the extent that even the dose of 10.0 mg of Old Tuberculin failed to produce a reaction, but apparently it was not sufficiently potent to resist the increased doses of reinfection emanating from the infecting case shortly before death.

The second case demonstrated the importance of sustaining the potency of immunity on a certain level, which apparently is another essential epidemiological factor. Immunity was efficient previously in protecting the patient against the implanted primary infection, but when its level was lowered by an attack of measles the exogenous infection was victorious. It is of significance that the "control" case, the other twin sister who avoided measles, succeeded in maintaining her immunity on the previous effective level.

## GROUP 3 NEGATIVE TUBERCULIN REACTORS WITH LOW IMMUNITY

In a previous report (2) we have presented findings on 46 previously negative reactors which later yielded evidence of tuberculous disease, both active and arrested. Since the publication of this report we have collected another series of 24 cases of the same type. Inasmuch as a detailed analysis of the conditions under which the 46 negative reactors of this type developed clinical tuberculosis was given in the previous report (2), we shall discuss at present only some of the most important facts elicited during the study of the additional cases.

Of the 24 primarily negative reactors of this group, 7, or 29.1 per cent, were whites, 16, or 66.6 per cent, Mexicans, 1, or 4.1 per cent, Cuban. Fourteen, or 58.3 per cent, were females, 10, or 41.6 per cent, males. Fourteen, or 58.3 per cent, were children up to 14 years, 10, or 41.6 per cent, above 14 years.

In one family there were 3 cases of this type, in another family, 2 cases, in 19 families there was 1 case in each.

The diagnoses and prognoses, after clinical tuberculosis became evident, were as follows: childhood tuberculosis arrested, 7 cases, all remained stationary, childhood tuberculosis active, 8 cases, with a very favorable progress in all of them, 4 became arrested, 2 showed a complete and 2 a partial absorption of the lesions, minimal pulmonary tuberculosis active, 6 cases, of which 3 became arrested, 1 clinically improved, 2 remained stationary and were placed in a sanatorium, moderately advanced pulmonary tuberculosis with a cavity, 1, there was no further information about the progress of this case, far advanced pulmonary and miliary tuberculosis, 1 of each, both died.

We feel that it would be of interest to compare the exposure to infection of this group totalling 70 patients in both series, previously reported and recently collected, characterized by low immunity, with the 90 patients of group 1 with high immunity. We wish to repeat once more that both these groups consisted of primarily negative reactors with a widely divergent consequent clinical course.

Several different criteria were used in this comparison: (a) the type and stage of the disease in the infecting cases, (b) the percentage of cases with sputum positive for acid-fast bacilli on direct smear, (c) the percentage of eventual deaths, (d) the length of exposure. Not wishing to encumber this paper with statistical details we shall only state that the reactors of group 3, those that eventually developed tuberculosis, were as a whole exposed to somewhat larger doses of infection than the re-

actors of group 1, those that as a rule have remained persistently negative to high doses of tuberculin. Nevertheless, this slight excess of infection does not in our opinion explain the tremendous difference in the ultimate fate of the respective exposed reactors. Apparently the difference in the individual immunity was by far the greater factor. This observation is indirectly confirmed by the well known fact that in certain instances some members of the same families develop active tuberculosis while others, though exposed to the same infection, persistently fail to react to tuberculin.

#### GROUP 4    NEGATIVE REACTORS SUBSEQUENTLY BECOMING POSITIVE AND REMAINING IMMUNE

It is a common experience that many individuals, for some time negative to tuberculin, eventually acquire a positive reaction without developing any clinical or roentgenological evidence of tuberculous disease. One is tempted to assume that apparently their inherent immunity during the negative phase of their tuberculin record previous to the implantation of primary infection suffices to prevent such implantation for a certain length of time and later, when the implantation of infection takes place, the inherent and the added acquired immunity are potent enough to localize the attacking microorganisms and to protect the host against the development of active disease. We must keep in mind that at one time all known positive reactors were negative and that the negative phase of their tuberculin record has remained unknown due to a certain timing of the application of the tuberculin test. In this sense, then, most of the known positive reactors belong to group 4. Inasmuch as the known negative phase of the tuberculin record of the individuals of this group is of a secondary epidemiological importance to the positive phase, we shall limit our present discussion to the above short statement. We hope to have an opportunity to report in the near future some material pertaining to the positive phase of the tuberculin record of this group.

#### DISCUSSION

The classification of the negative tuberculin reactors used in this paper was devised for the study of our material only. We do not suggest it as a basis for classification of the negative tuberculin reactors in general.

For reasons just stated, group 4—the negative reactors that later became positive—was not studied in detail in this paper.

It seems that the main interest in the study of the negative reactors

is centred around the first three groups. Facts pertaining to each of these groups were brought out in the respective parts of the paper. We wish to discuss here briefly some epidemiological phenomena generally observed during the study of negative tuberculin reactors and applicable in varying degrees to the three first groups.

It seems that it is essential for the potency of immunity to be sustained on a certain level. If this level is lowered by various factors, among which intercurrent infections play an important rôle, disease may develop. However, in many instances the newly implanted tuberculous infection brings into action the reserve forces of immunity which are sufficiently potent to prevent the development of the disease and in some cases even to eradicate the invading infection after it succeeded to penetrate into the tissues of the host. This is manifested by the cycle in which specific skin hypersensitiveness moves in certain cases, from a negative tuberculin reaction to positive and back again to negative. This feature of relativity of immunity is also evident with regard to the dosage of infection. It seems that the efficiency of immunity in each individual case is apparently limited to a certain dosage of infection and does not function beyond this limit. In practice it is impossible to determine this limit, obviously because there is no way to measure more or less exactly the dosage of infection and especially the degree of immunity. We know only that this level is individually different. We may also surmise that this level is highly dependent on the amount of the reserve forces of immunity which can be developed by the host under the attack of the increased infection. It seems that efficient function of immunity depends in some cases on the frequency and regularity of the exposure to infection. Immunity may function efficiently in the presence of exposure but may become dormant later when the exposure either ceases completely or decreases, so that when the host is suddenly exposed again to a potent dose of infection there is not enough time to bring into action all the reserve forces of immunity, and disease may develop.

As it can be seen, the study of the function of immunity under varied conditions invariably brings to the front the problem of its reserve forces.

It is true that disease cannot develop in the absence of infection. The dosage of infection, its virulence, frequency, the intimacy and regularity of exposure are factors of paramount epidemiological importance. Nevertheless, in evaluating the rôle of all factors involved in the development of the disease, it seems that in many instances the factor of immunity is of greater epidemiological significance than the factor of infection.

One may say that the ultimate fate of the individual exposed to infection depends on factors working rather within than without his own body. This observation can also be interpreted in the sense that there is a very wide divergence in individual resistance.

It seems to us that conclusions derived from this study should not be considered as limited to negative tuberculin reactors. We hope to report later findings on positive reactors supporting this opinion. However, all these conclusions are brought to light much more clearly in the study of the response of the negative tuberculin reactors to exogenous infection than of that of positive reactors because of the more conspicuous changes in the tuberculin record, especially when these changes are correlated with the clinical picture.

As we have seen, the different types of negative tuberculin reactors vary in the potency of immunity possessed by them. In practice it is impossible to foretell to which group an individual negative tuberculin reactor will eventually belong.

Only time will reveal whether this reactor will remain well, uninfected or will succumb to disease. We still lack a reliable immunity test which could be helpful in the practical epidemiological field work. Therefore, in our opinion it behooves the field worker to watch very carefully all negative tuberculin reactors as potentially belonging to group 3 and thus susceptible to disease till in time a sufficient proof to the contrary will be accumulated.

It seems to us that, in the absence of a specific test for immunity in tuberculosis, a careful coordination of data derived from the epidemiological studies of the spreaders of infection and from the tuberculin and clinical records of the exposed "contacts" would be valuable in determining the degree of immunity possessed by these contacts. Naturally, to be of value the clinical and tuberculin records must contain data accumulated over a reasonable length of time.

In conclusion we wish to state that we realize fully that many important epidemiological problems in tuberculosis are far from being clearly understood. We are aware of the great differences in opinion on this subject existing among workers in the field of tuberculosis. Therefore, the opinions expressed by us in this paper are presented here only as personal impressions based on the accumulated reported material. We feel that presentation of such observations of facts and of personal opinions may be of some value as material for further studies and discussions.

## SUMMARY AND CONCLUSIONS

For convenience of study, the negative tuberculin reactors were divided into four epidemiological groups

- 1 Persistently negative reactors with high immunity
- 2 Negative reactors with a record of spontaneous desensitization following a period of tuberculoallergy
- 3 Negative reactors with low immunity
- 4 Negative reactors later acquiring tuberculoallergy and possessing adequate immunity during both phases of their tuberculin record

The opinion was expressed that immunity varies greatly in each of the above groups, that at best it is relative and that its efficiency depends on many exogenous and endogenous factors, among which exposure to tuberculous infection is of a great importance. It seems that, in general, successful resistance to disease depends a great deal more on the function of specific immunity than on the degree of exposure to infection.

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## THE DETECTION OF TUBERCULOSIS IN GROUP SURVEYS

PHILLIP T KNIES<sup>1</sup>

There is, of course, no question of the fact that for maximum accuracy in the detection of tuberculosis every possible diagnostic procedure should be available. Such an ideal, however, is at present impractical of attainment in the examination of large groups of individuals. General expense, the lack of adequate physical equipment, and often of trained personnel, are potent limiting factors in such work despite the value and necessity of multiple procedures in selected individual cases. In cognizance of these facts several plans of survey have been suggested (1, 8, 13, 14, 10), each representing some compromise between expense and efficiency, but best calculated in the opinions of their respective proponents to serve in the detection of significant disease. The truly superior procedure has not yet been identified, for many considerations in the interpretation of data so obtained remain yet in the theory of tuberculosis pathogenesis and immunology. Continuation of methods emphasizing immunological reactions on the one hand, and radiological findings on the other is desirable as a means of critical evaluation of each (9).

Probably the routine most widely used in this country consists in a preliminary "screening" of suspects, particularly children, adolescents and young adults by tuberculin testing, followed by roentgen examination of only the positive reactors. In spite of valuable information, particularly of an epidemiological character, obtained in this way, it has appeared to the author that this procedure involves an inherent error of considerable magnitude, in that certain cases negative to tuberculin may yet show findings significant of tuberculous infection by roentgen examination. Such error has been admitted by advocates of this routine of mass examination for tuberculosis, but has been considered of insignificant proportion (8, 11). In the author's experience, however, the number of such instances occurring in a clinic<sup>2</sup> where both methods of examination were routinely applied appeared impressive, and the present study was

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undertaken to determine the degree of error which might be avoided by such combined examination in contrast with the findings of either method alone

Two groups of individuals are included in the present study. The first consists of 206 persons, ranging in age from five to seventy-five years, otherwise unselected except that they were consecutive cases showing X-ray findings significant of tuberculous infection. Usually such findings comprised calcification at the hilum, or in the parenchyma, or both, though there was occasionally included a patient with frankly exudative pulmonary infiltration, but none with involvement beyond minimal, and none with cavitation. These exclusions were observed in an effort to

TABLE 1\*

*Results of tuberculin testing by intracutaneous use of OT in 206 cases showing radioscopic evidence of tuberculous infection, subgrouped according to age*

AGE	FIRST TESTS	NEGATIVE	+	++	+++	++++	CASES LOST	SECOND TESTS	NEGATIVE	+	++	+++	++++
0-5	4	2	2				2						
6-10	22	13	5	3	1		4	9	4	3	1	1	
11-20	73	45	12	14	2		14	31	12	11	8		
21-30	37	19	10	8			4	15	1	6	3	5	
31-40	42	24	9	7	2		6	18	5	7	5	1	
41-50	18	7	7	4			3	4		1	2		1
51-60	6	3	2	1			1	2		2			
61-70	3	1	0	2				1			1		
71-75	1		1										
0-75	206	114	48	39	5		34	80	22	30	20	7	1

\* Note cases lost between first and second tests

minimize a possible error on the basis of anergy induced by extensive, progressive lesions. This selection also militated to some degree against the most favorable showing by radiological methods which, of course, miss few, if any, advanced pulmonary lesions. It may be admitted, of course, that ultimate diagnosis requires more than X-ray determination of infiltration. Cases with doubtful calcifications were considered as noncalcific.

Tuberculin skin tests were then made by the intracutaneous technique, 0.1 mg of commercial OT being employed as the first dose, followed in one week by 1.0 mg if the reaction had been negative or equivocal. Reactions were graded by the standard criteria, considering the total wheal and central oedema (17).



Physical examinations were also given each patient, but the results are not included in the present analysis, inasmuch as it is generally conceded that, as routinely accumulated, such data are inferior to those of the other two methods, and may best be utilized for the further careful study of those individuals already diagnosed, that is, in determining relative

TABLE 2

*Distribution of positive and negative reactions to PPD and OT in 317 consecutive cases subgrouped according to presence (+) or absence (—) of tuberculous foci at pulmonary hilum (H) and in pererchyma (P)*

CALCIFICATION	TUBERCULIN REACTION	OT 0.1 mg	PPD 0.0002 mg	OT 1.0 mg	PPD 0.005 mg
H+ P—	+	24	14	7	8
	++	14	8	6	3
	+++	7	3	2	2
	++++	0	0	0	0
	—	28	48	10	12
H— P+	+	3	2	1	3
	++	1	0	0	0
	+++	1	0	1	0
	++++	0	0	0	0
	—	5	8	2	1
H+ P+	+	34	33	19	15
	++	44	16	9	4
	+++	21	21	4	2
	++++	2	2	0	0
	—	84	113	28	39
H— P—	+	14	6	6	10
	++	7	5	1	2
	+++	3	2	0	0
	++++	0	0	0	0
	—	25	36	21	16
		175 (55%)+	112 (35%)+	56 (48%)+	49 (42%)+
		142 (45%)—	205 (65%)—	61 (52%)—	68 (58%)—

aeration, bronchial obstruction, etc. Data pertaining to this group of persons are presented in table 1

The second group of individuals comprised 317 consecutive clinic patients with or without X-ray evidence of lesions significant of tuberculous infection and excluding only advanced cases of disease for reasons noted before. Ages were not noted among these patients, but subgroup-

ing is possible on the basis of the absence or location in the chest of the significant X-ray lesion, usually calcification

These patients were then tested with Mantoux technique, introducing simultaneously into the skin of one forearm 000,02 mg of Purified Protein Derivative and into the other 1 mg of OT. In cases where both tuberculin tests were negative, or one was negative and the other equivocal, or both were indeterminate, second tests were done in one week, employing 005 mg of PPD and 1.0 mg of OT.

As in the first group physical examinations were done, but not included in the present analysis. Data pertaining to this second group of cases

TABLE 3

*Comparison of degree of reaction to PPD and OT in 317 consecutive clinic cases unselected except for elimination of advanced tuberculous infiltrations. The lower line of figures notes cases reacting positively to one tuberculin but negatively to the other*

OT 0.1 MG > PPD 000.02 MG	OT 1.0 MG > PPD 005 MG	OT 0.1 MG = PPD 000.02 MG	OT 1.0 MG = PPD 005 MG	OT 0.1 MG < PPD 000.02 MG	OT 1.0 MG < PPD 005 MG
110	35	178	71	29	19
OT+ PPD-	OT+ PPD-			OT- PPD+	OT- PPD+
76	21			12	13

TABLE 4

*Correspondence of detection (+) and nondetection (-) of tuberculous foci among 317 persons by tuberculin testing with both PPD and OT, and by fluoroscopy*

TUBERCULIN + FLUOROSCOPY +	TUBERCULIN + FLUOROSCOPY -	TUBERCULIN - FLUOROSCOPY +	TUBERCULIN - FLUOROSCOPY -
210	31	59	16

are presented in tables 2, 3 and 4 and are combined with those of the first group in table 5

In the radiological evaluation of both groups the fluoroscope was employed with corroborative single films wherever interpretation appeared questionable. Fluoroscopic findings have been shown in previous studies by the author (10) and others (5, 6, 7, 14) to be dependable when compared with films. In this connection it may be added that in the determination and localization of calcifications, particularly at the hilum, fluoroscopy is, in the author's opinion, a method superior to the flat or single X-ray film. In such films there frequently occur well defined,

smooth-bordered densities in the hilum zone of the lungs which may be difficult to interpret as between small calcifications and long-axis views of trunk markings or of vessels filled with blood. Such difficulty rarely arises or is usually easily solved by fluoroscopy by slight rotation of the patient, or movement of the tube, or observation in various phases of respiration, especially in forced expiration which serves to empty large central vascular channels. The ease of examination of the retrocardiac area is also a decided advantage of fluoroscopy as pointed out elsewhere (10). On the whole, in experienced hands and with adequate equipment fluoroscopy appears to be a thoroughly dependable method of radiological chest examination. Possibly its gravest fault is the absence of permanent, objective records.

The commonest X-ray evidence of past tuberculous infection is calcification as seen in the Ghon tubercle or the Ranke complex (4). In the

TABLE 5

*Distribution of degree of reaction in 474 first tests of OT 0.1 mg. and in 169 second tests of OT 1.0 mg.*

REACTION	OT 0.1 MG.	OT 1.0 MG.
--	231	62
+	109	57
++	98	35
+++	34	14
++++	2	1

present study it has been assumed, as is generally done, following the work of Opie that all such formations are of tuberculous origin, though a minor objection to this conclusion may be raised in view of the occasional occurrence of calcification in the healing of other inflammatory and destructive pleural and pulmonary lesions (3). The common assumption that calcific lesions are always significant of a first-infection type of tuberculosis would also appear questionable in view of the similar appearances of calcifications shown by serial observation to result from reinfection types of disease. Of course, not every tuberculous infiltration, either primary or secondary, leaves calcification as evidence of its previous existence, many completely disappearing or showing only fibrous transformation. In addition to this group a certain small percentage of cases will be undetected by roentgenological studies because the lesions are extrapulmonary.

## DISCUSSION

Data pertaining to the first group of patients are analyzed in relation to age groups in table 1'. In those subgroups containing a sufficient number of individuals to permit statistical evaluation it is interesting to note that the percentages of positive and negative reactions to the initial tests were highly constant despite age. This is contrary to the common opinion that increased time after tuberculous activity is associated with reduced sensitivity to tuberculin. A similar constancy is noted in the results of the second tests. These observations suggest that, with increasing antigenic potency attained by variation of type or increased amount of tuberculin injected, an approach should be made to a 100 per cent standard represented by the entirety of a group of infected or formerly infected persons. In the present analysis, as already pointed out, the X-ray demonstration of a significant lesion or calcification is taken as indicative of such infection, and with increasing dosage or potency one might therefore expect positive tuberculin results in all of the present selected group. This attainment is, of course, limited by the number of infected persons whose reactivity has dropped or remained below a threshold level to a reasonable dose of tuberculin. Such unresponsive cases are often assumed to be inactive from the standpoint of tuberculous disease, although of the 317 patients of group 2, 7 were found showing negative tuberculin reactions despite minimal exudative infiltration proved tuberculous by subsequent observation. Furthermore while the assumption of tuberculous inactivity in tuberculin-negative reactors may pertain more or less accurately to current clinical disease, it does not necessarily extend to future pathogenicity. The recent work of Feldman and Baggenstoss (16) in demonstrating the sterility of calcified encapsulated tuberculous lesions is important in this regard. It would appear, however, to be quite as important from the individual and clinical view point, as well as from the epidemiological approach, to know not only the cases responsive to certain arbitrary tuberculin dosages, but also those with nonreactive infection or disease detected by other objective methods, in this instance radioscopy. Claims made for tuberculin testing have usually referred to its value in the detection of infection as distinct from disease. Its demonstration of activity of disease has appeared less dependable. Similar claims can, of course, be made for radiographic methods except in cases with extrapulmonary or noncalcitrizing infection, but with the added advantage of a keener index of clinical activity of the lesions found. It would appear to be important

in survey work, whether for the detection of clinical disease or of infection only, that that method of examination be used which will most inclusively present both infection and disease for further study. A greater number of inactive infections brought to careful scrutiny would not be objectionable especially in view of other clinically active cases also detected which might have remained unrecognized by another method of examination.

Considering the first tests of all patients of group 1, it is seen that of these individuals with definitely calcific foci 55 per cent failed to respond, 25 per cent showed a mild reaction, 19 per cent a moderate reaction and 2.4 per cent a severe reaction. A similar gradation of results pertained to all age subgroups.

Of the second tests 27 per cent remained negative, while 37 per cent showed mild, 25 per cent moderate and 10 per cent intensely positive reactions. Twenty-two cases remained negative to both tuberculin tests, these comprise 25 per cent of the cases submitted to second tests and 11 per cent of the original 206 patients examined. This group constituted a low percentage of nondetection. With it, however, should be considered a second source of error, not usually included in the statistics of such studies, but apparently occurring in the experience of others (2) as well as of ourselves. Thus of the 114 patients nonreactive to the first tests, only 80 were returned for reexamination by the second test, 34 cases thus being lost, or 16 per cent of the original group of patients. This loss from an entirely voluntary group was in spite of an excellent follow-up system, and was in large measure due to the objections of patient or parent to a repetition of the test. While obviously these cases cannot be charged against the scientific accuracy of tuberculin testing, they do constitute an important source of error in its practical application. Thus if one combines with the cases negative to both tuberculin tests those lost between tests, there is a resultant error of 27 per cent of the original group of patients. Such a figure is of considerable practical importance in the examination of large groups.

The second group of patients by reason of the nature of the material and tests permits a wider analysis than the first, and the testing with both tuberculins permits contrast of their results pertaining to this group. That such simultaneous application of tests is without notable effect on their results has been shown by McCarter, *et al* (2).

In table 2 all cases of this group are arranged as to the presence or absence of pulmonary calcification and its location, if present, in terms of

hilar or peripheral position. Thus "H-positive P-negative" indicates that calcification was detected at the hilum, but that no parenchymal lesion was discovered. Other subgroups are then easily understood. These groups are then further subdivided according to the degree of reaction to tuberculin as above noted.

It is seen that in all groups and to both types of tuberculin the greater percentage of positive tests were of the mild type with gradation to the more severe ones. It is further interesting to note again the constancy of positive to negative reactions in all groups, though at different levels for the two types of tuberculin. Thus in the first tests 56 per cent of cases reacted positively to 1 mg of OT as against 35 per cent with 000,02 mg of PPD. Of the second tests 48 per cent were positive with 1.0 mg of OT as against 42 per cent with 0.05 mg of PPD.

Such observations are susceptible to two interpretations. Thus the test resulting in the higher percentage of positive reactions may be the more accurate inasmuch as it more closely approaches a theoretical maximum. On the other hand, such a test may be giving a greater number of false positive reactions. Under the conditions of the present experiment, at least, the particular preparations of OT used appeared more capable than was the PPD of eliciting a response expected on the basis of X-ray findings. According to the above interpretations this would be equivalent to its greater accuracy. The author is fully aware, however, of the possible inconstancy of such potency as a result of varying methods of preparation of OT. Several brands of OT have, however, all appeared more reactive than the presumably equivalent doses of PPD.

A second observation of interest is the fact that the percentage of positive and negative reactors in groups of statistical size appear to be independent of the location of calcification within the lung or even its complete absence from the chest. It is possible, of course, that extrapulmonary foci may serve in part to maintain responsiveness to tuberculin, but it remains notable that no significant variation of sensitivity can be discerned.

Such observations suggest that the conditions actually being detected by radiology on the one hand and tuberculin tests on the other may be largely independent. Thus radiology is employed in the detection in the lungs of inflammatory products of exudative, fibrous or calcific nature without reference to allergy or anergy. Tuberculin testing, on the other hand, is presumed to detect conditions of sensitivity to tuberculin. It

would appear that, in view of the significance of both these types of information, it would be impracticable from the standpoint of clinical or epidemiological considerations to use either method alone as a screen

It will be noted that the percentage of reactions positive to 0.1 mg of OT in all cases of group 2 is 10 per cent higher than that in group 1 above, while the percentage of reactions positive to 1.0 mg of OT is 25 per cent less in group 2 than in group 1. The causes of such inconsistency are not apparent, but may be found in the variables surrounding tuberculin testing, especially with OT.

A rearrangement of the data of the second group as in table 4 shows agreement between fluoroscopy and tuberculin testing to the extent of 66 per cent in terms of positive reactions, and 5 per cent in negative reactions. This comprises a total agreement of 71 per cent. Cases reactive to tuberculin, but without fluoroscopic evidence of infection, constituted 9.7 per cent, while cases showing fluoroscopically significant lesions, but negative to tuberculin testing, comprised 18.6 per cent. This latter figure is more than three times greater than a comparable one found by McPhedran and Opie, quoted by Long (8), and included seven instances of exudative infiltration with negative tuberculin reactions. It is thus apparent that approximately a 9 per cent greater error would be incurred in this group by examination with tuberculin alone than would result from fluoroscopy alone. It should furthermore be recalled that the tuberculin tests referred to here are double ones, including in each instance both OT and PPD, a test being considered positive if only one responded. As will be shown later, there is further disagreement between results to these tuberculins themselves, so that in actual practice the percentage of error in tuberculin testing alone would exceed that in fluoroscopy alone by something more than the 9 per cent of this experiment. It is, of course, obvious that the accuracy of the combined use of tuberculin and fluoroscopy exceeds that of either alone.

If the data of group 1 be combined with those of group 2 pertaining to the reactions to OT without reference to the PPD, it is seen that of a total of 474 cases examined, all of which had been shown to have radioscopic evidence of tuberculous infection, 49 per cent gave reactions negative to 0.1 mg of OT while 37 per cent of 169 second tests gave reactions negative to 1.0 mg of OT. This latter group, negative to both tests, constitutes 13 per cent of the original 474 cases examined. If a proportional number of the 28 cases lost in the first experiment between the first and second tests and of the 34 cases so lost in the second experi-

ment were considered as positive or negative, the total percentage of error would, of course, be still higher. As pointed out above, however, all such lost patients should be considered an inherent error of the method. The 62 cases thus lost in the combined groups comprise an additional 15 per cent error, raising the total actual deficiency of tuberculin testing in terms of positive fluoroscopic diagnosis to 26 per cent, under the conditions of the present experiment. That is, tuberculin testing as ordinarily applied with OT has failed in this experiment to detect 26 per cent of the cases of tuberculous infection recognized by fluoroscopy while in the available group, the opposite is the case in only 9.7 per cent. It is obvious that such an error must be of considerable significance, whether in detection of active clinical disease or in study of the epidemiology of the infection.

The failure of tuberculin testing in such a percentage of cases would appear to constitute a serious objection to such large group investigation for tuberculosis as suggested by Stewart (13). The not infrequent observation of cases with pulmonary calcification and with tuberculin tests negative on one examination, but positive later without radiological change, would seem to be a further drawback. It is to be expected of such a biological reaction as the tuberculin test that it would show variation in sensitivity which at times might become so low as to be subthreshold to a given dose of tuberculin which might later give the response expected in the first test. It would not appear necessary to explain every such occurrence on the basis of sensitization by tuberculin itself, or even by the augmentation of a preexisting subliminal sensitivity by the tuberculin.

Turning again to the data of group 2 in table 3, relative to the comparative effectiveness of OT and of PPD it is apparent that at least the brands of OT used were more sensitive than the PPD. Thus among the first tests by both tuberculins, 56 per cent of cases showed equally positive or negative reactions. In 35 per cent of cases the OT was more decisive than the PPD while the opposite was true in only 9 per cent. Of the second tests, 57 per cent of results were equally positive or negative, while 28 per cent showed reactions more decisive to OT than to PPD with 15 per cent the opposite. If one considers from among such cases of disagreement those in which one tuberculin gave a positive reaction and the other a negative one, it is seen that 24 per cent of the total number tested would have been overlooked in the first test if only PPD had been used. The error in case only OT had been used would have



been 4 per cent. Among the second tests the percentages would have been 17 per cent against 10 per cent. It is therefore clear that a considerably greater number of cases were detected by OT than by PPD under the conditions of this experiment. As pointed out above this may be correlated with greater specific sensitivity rather than with excessive false positive results. The difficulty of interpretation of such data has been noted by others (15), and the above findings have not been universal (12). It may further be noted that the two cases of necrotic ulceration seen in the combined series were both with PPD.

#### CONCLUSIONS

1 Two experiments are recorded, contrasting the results of tuberculin testing and fluoroscopy as methods of mass survey for detection of tuberculous infection.

2 It is apparent that, while for neither method can complete accuracy be claimed in terms of the other, error would be less in these experiments with fluoroscopy alone than with tuberculin testing alone.

3 It is apparent that the "tuberculin screen" so widely used in survey work may be subject to an error approximating 25 per cent in its epidemiological application.

4 A routine of examination, consisting in simultaneous tuberculin testing and fluoroscopy, is subject to less error than is incurred by the use of either method of examination as a "screen" for the other. The combined use of both methods would appear desirable in clinical as well as epidemiological surveys in view of this greater general accuracy, as well as in view of 7 cases showing exudative lesions, roentgenologically, but negative tuberculin reactions.

5 Under the conditions of the present experiment, OT was appreciably more sensitive than PPD.

6 Sensitivity to tuberculin does not appear dependent upon location or even absence of pulmonary calcification, thus suggesting a divergent significance of the two types of findings, and again the desirability of routine use of both methods of examination.

7 By the use of fluoroscopy the cost of reliable radiological examination is not prohibitive to its general application.

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## TUBERCULOSIS SURVEY OF AN ENTIRE COMMUNITY<sup>1</sup>

ROBERTS DAVIES AND C A SCHERER

During recent years several studies have emphasized the importance of tuberculosis surveys of the whole population of a community. The State Department of Health of Tennessee has reported such a survey of the Negro population of Kingsport, and Wells and Smith have reported a similar study in Kingston, Jamaica. In Detroit the public health nurses are instructed to urge the entire population of certain areas with a high tuberculosis mortality to be examined.

In addition to the collection of scientific data, such surveys are of immediate practical importance. They permit the discovery and isolation of all the foci of tuberculous infection in a community. They uncover early cases of disease that may be treated while their prognosis is still good. They identify those cases of apparently inactive disease that should be repeatedly checked for evidence of activity. It is extremely doubtful that any other method will fulfill the same functions to the same degree.

This paper is a report of a study of the whole population of a township in St. Louis County, Minnesota, with the emphasis on finding new cases of active tuberculosis. The population of the community is 367. With the exception of a few families, they are all of Finnish birth or descent. Sixty-five per cent of the population is foreign born. The people earn a living chiefly from their farms. The soil is poor and the economic status of the community is low.

Our procedure was to visit each house in the community, explain the purpose of the survey, take a brief history of the family, and give Mantoux tests to everybody. PPD was used for all skin tests. The usual first-strength dose of 0.000,02 mg. was used for the first test, and all who did not react within forty-eight hours were retested with one-half the usual second strength dose, or 0.002,5 mg. We used the weaker solution because we were afraid that a few severe reactions, such as have been reported frequently from the full second-strength dose, might lose us

<sup>1</sup> From the Nopemng Sanatorium and the St. Louis County Health Department, Nopemng, Minnesota.

the full cooperation of the community. All positive reactors were taken to the Sanatorium for X-ray films. Single chest plates were taken at 72 inches with 0.1 second exposure, using 100 milliamperes and from 66 to 90 kilovolts, depending upon the thickness of the chest. All films were interpreted by Dr. G. A. Hedberg of the Sanatorium staff.

Of the 367 people in the community 66 were not adequately examined. Nine refused to be tested, 29 could not be contacted, 10 with positive Mantoux tests were not X-rayed and 18 with negative first-strength Mantoux tests were not examined further. The distribution of positive Mantoux tests and the various X-ray findings are not essentially different from those of other surveys. Sixty-two per cent of the males and 57 per cent of the females examined had positive tuberculin reactions. One-third of these positive cases reacted to the second test only, 123 of 218 X-ray films taken were negative for tuberculosis. There were 56 cases showing only healed primary tuberculosis and no cases of active primary tuberculosis. Thirty-two cases of healed tuberculosis of the adult or reinfection type were found, of which 25 were minimal, 5 moderately advanced and 2 far advanced. Half of these inactive cases were negative to the first Mantoux test. Of course, all the cases in young people and any others classified as inactive in which there was any suspicion of activity were filed for future check-up.

The important result of the survey was that 6 previously unknown cases of active tuberculosis were found, 2 of these had positive sputum. One of the cases was far advanced and the other 5 were moderately advanced. All of them were immediately hospitalized and treated. At the present time, less than a year after the completion of the survey, 5 of these 6 cases have returned home and are classified as arrested. The one remaining case will soon be ready for discharge. These 6 cases were diagnosed early (with the exception of the single far advanced case) and removed from the community. Four of them were hospitalized before they became a menace to others. They have been treated satisfactorily with a minimum expenditure of time and money and have been returned to their homes in good health.

The cost of this survey, including salaries, was approximately \$1000.00. Assuming that the average early case requires one year less treatment than the average far advanced case, and that the cost of treatment is \$1000.00 a year, by finding 5 early cases we saved the county \$5000.00. This is without considering the economic value of isolating these cases and preventing further infection of the community.

Since, on the basis of previous sanatorium admissions, we expected to find an unusual amount of disease in the area we studied, one might object that in only a few communities would there be enough tuberculosis to make the same method practicable. We have therefore tried to compare our results with those of other surveys of similar communities, that is, rural communities with predominantly white population. Such comparison is difficult because we can find no other survey of a similar community which has attempted to examine the whole population and the methods of sampling are not outlined in the published reports. Also, most extensive surveys have not included X-ray films and most other workers have used Old Tuberculin instead of PPD. We do not

TABLE 1

*Percentages of positive Mantoux tests in various surveys (all percentages corrected to age distribution of "normal" population)*

INVESTIGATOR	POPULATION STUDIED	PERCENTAGE POSITIVE
Korns, Sydenstricker, Downes	Part of white population of Cattaraugus County, New York	40.1
Aronson	Part of population of rural communities in Michigan	49.4
Aronson	Part of white population of rural communities in the South	64.7
Davies, Scherer	Total population of rural township in Minnesota	63.9*
Hilleboe	Admissions to Minnesota State Institutions excepting the State Tuberculosis Sanatorium and the Orthopedic Hospital. Tested with 1 mg. OT only	Male 49.4 Female 41.4
Davies, Scherer	Total population of rural township in Minnesota. First Mantoux only	Male 52.5 Female 37.5

\* All persons X-rayed without Mantoux test considered as positive

know accurately how our second-strength test of one-half the usual second dose of PPD compares with their tests. Nevertheless, the comparisons shown in table 1 may be considered suggestive and would seem to indicate that a survey of the total population might profitably be used in other communities. Of course, in an area as comparatively free of tuberculosis as Cattaraugus County, New York, where only one active case was found in over 800 X-rayed, such a survey would not be practical.

It is interesting that only 3 of the 6 active cases found in this survey gave a history of contact with a previously diagnosed case. The other 3 would have been missed by any examination of contacts of sanatorium

admissions, no matter how thoroughly it was done. Also, none of the 5 early cases had any symptoms whatever and would not have reported to a physician until their disease was further advanced.

Everyone feels that case-finding efforts are necessary to remove foci of tuberculosis from a community and to get early cases under treatment while their prognosis is still good. Examination of contacts is probably the most efficient case-finding method since it will presumably give the greatest results for each dollar spent. However, in some areas with a high incidence of tuberculosis a more thorough method seems necessary, and for such communities a Mantoux survey of the whole population with X-ray films of the positive reactors may perhaps be a practical and valuable procedure. We should like to see this method tested in other communities with a high incidence of tuberculosis.

#### CONCLUSIONS

- 1 By a Mantoux and X-ray survey which included 301 out of 367 residents of a township, 6 new cases of active tuberculosis were found.
- 2 The cost of the survey was slight compared with the economic value of the results.
- 3 The value of the method should be further tested in other communities where the incidence of tuberculosis is high.

We wish to thank the following members of the staff of Nopeming Sanatorium and the St. Louis County Health Department for their cooperation in this survey: Dr. A. T. Laird, Dr. G. A. Hedberg, Dr. L. H. Stahly, Dr. P. C. Welton, Dr. Karl Pfuetze, Mr. Charles Robb, Miss Elizabeth Muckala, Miss Leah Keable, Miss Elma Huttula, Miss Alice Larson, Mr. Charles Haver, Mr. Fred Provencal, Miss Berde Haugerude, Miss Edith Unkenholz, Miss Edith Seglem, Miss Margaret Lundgren, Mrs. Irene Joyce, Mrs. Harold Morkved, Mrs. Mayme Thompson, Miss Berenice LaLiberte and Miss Margot Devich.

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## THE EFFECTS OF ULTRAVIOLET RADIATION ON TUBERCLE BACILLI<sup>1</sup>

KLNNETH C SMITHBURN AND GEORGE I LAVIN

Among workers studying tuberculosis the interest in ultraviolet radiation has centered chiefly on its clinical application. However, it was early recognized that the sun's rays have lethal effects on tubercle bacilli, and subsequently shown that this action was chiefly due to rays in the ultraviolet region. A review of the earlier studies on the clinical use of ultraviolet radiations, and on the effects of these radiations on tubercle bacilli, was published in 1921 by Mayer (1). In 1924 Mayer and Dworski (2) employed rather weak but not well standardized suspensions of tubercle bacilli and found that the organisms were killed by as little as three minutes' exposure at a distance of 5 inches, by the radiation emitted from a quartz mercury vapor lamp. Howze (3) found that tubercle bacilli were killed in five minutes by the radiation of a mercury vapor lamp, but he did not standardize the suspensions and his experiments cannot be regarded as quantitative. Eidinow (4) observed that saline suspensions containing 1 mg of tubercle bacilli per cc were rendered nonvirulent by ten or fifteen minutes' exposure to the mercury vapor lamp and believed the rays shorter than 3,300 Å to be the most effective. A year later Mayer and Dworski (5) reported that suspensions containing 2,750,000 tubercle bacilli per cc, exposed at a distance of 2.5 cm from the window of the lamp, were reduced in pathogenicity in two or three minutes and were made nonvirulent by four minutes' exposure.

Our interest in this subject was stimulated by the work of Stanley (6), Hodes, Lavin and Webster (7), and Kidd (8). Stanley (6) showed that tobacco-mosaic virus protein could be rendered avirulent by ultraviolet radiation, while the immunological activity was retained. Kidd (8) likewise found that the infectivity of the Shope papilloma virus could be abolished by means of ultraviolet radiation without loss of complement binding capacity. Hodes, Lavin and Webster (7) made

<sup>1</sup> From the Laboratories of The Rockefeller Institute for Medical Research, New York City.

different application of the same principles, they found that the infectivity of rabies virus could be eliminated with ultraviolet radiation, and that if the exposure was quantitatively proper the inactivated virus was still able to induce immunity to rabies in mice

Lavin and Stanley (9) found that the tobacco-mosaic virus protein had its maximum absorption at about  $2,650 \text{ \AA}$ . Burger (10) found that radiation in this range had much greater bactericidal action than did longer wave lengths, he also found that bacteria inactivated with ultraviolet rays made superior vaccines (11). Gates (12) later showed that the maximum absorption of *B. coli* was in the same approximate range and that similar radiation was highly effective in the inactivation of both *Staphylococcus aureus* and its specific bacteriophage (13). Furthermore Spiegel-Adolf and Seibert (14, 15) observed that various tuberculin preparations had absorption maxima at  $2,650 \text{ \AA}$ . A lamp was commercially available which had a maximum energy output in this approximate region. It was, therefore, decided to use this lamp to study the effect of its radiation on the immunizing potency of tubercle bacilli. Simultaneously, studies were made of the effects of the radiation on the viability and virulence of mycobacteria.

#### MATERIALS AND METHODS

**Ultraviolet radiation.** The source of radiation employed was a mercury vapor resonance lamp (manufactured by Hanovia Chemical Co., Newark, New Jersey). Approximately 90 per cent of the energy was emitted as radiation of  $2,537 \text{ \AA}$ . Suspensions of tubercle bacilli contained in quartz flasks were exposed to the lamp while being agitated in a mechanical shaker so arranged that the flask was at a constant distance (15 cm) from the source of radiation. During exposure the quartz flask was sealed with a close fitting gum-rubber cap. The physical set-up is described in detail by Hodes, Lavin and Webster (16).

Intervals of exposure were timed with a stop-watch. At the end of an interval the lamp was screened, the gum-rubber cap was removed from the quartz flask, and the sample of irradiated suspension was removed with a sterile pipette.

**Bacteria.** Two strains of tubercle bacilli were used in the experiments: a highly virulent line of the well known human strain H37, and a second human type strain designated Lockett, isolated from the cerebrospinal fluid of a patient with tuberculous meningitis (17). The organisms were grown on glycerolated egg-yolk medium adjusted to pH 6.8 (18). Vigor-



ously growing cultures, about three weeks old, were employed. Suspensions were prepared by grinding a weighed quantity of organisms, freshly removed from the tube, in a sterile porcelain mortar, with dropwise addition of sterile physiological saline solution in sufficient quantity so that 1 cc of suspension contained 1 mg of bacteria. Appropriate decimal dilutions were made from such suspensions to contain the desired quantity of bacteria. Suspensions to be irradiated were at once transferred to the sterile quartz flasks, and suspensions used for inoculation were employed promptly to minimize the sedimentation or agglutination of the organisms.

*Animals* Albino guinea pigs, bred in this Institute from stock free of epizootic streptococcal infection, were used in the experiments. Both males and females were used, but animals of different sexes were caged separately. In experiments where groups of animals were to be compared for longevity following inoculation, the groups were arranged either to contain animals of the same sex, or so that the distribution of individuals of different sex was the same in control and test groups. Also, groups to be so compared were comprised of animals of similar individual weights. For the most part the guinea pigs weighed about 400 g. Not more than 4 were caged together.

*Inoculations* All inoculations, whether for the purpose of testing the virulence of irradiated organisms, or to test the immunizing potency of vaccine, were made by the intracerebral route. Anaesthesia was induced with ether or by intraperitoneal injection of 0.5 per cent solution of Seconal<sup>2</sup> in saline. The dose of Seconal was 20 mg per kg. Intracerebral inoculations were done by the method previously described (19).

*Vaccinations* Irradiated suspensions containing 1.0 mg of bacteria per cc were injected subcutaneously along the right side. Injections were made daily for five days, the daily dose being 0.3 mg in 0.3 cc. In one experiment test inoculations were done eleven days following the last dose of vaccine. In the other experiment the animals were inoculated fifteen days following the last prophylactic injection.

*Tests of viability of irradiated suspensions* These were made by seeding tubes of the glycerolated egg-yolk medium with 0.2 cc each of suspension. In two experiments tubes were seeded in duplicate, in other experiments 5 tubes were seeded with each irradiated sample.

<sup>2</sup>-Sodium Propyl methyl carbonyl Allyl Barbiturate, Lilly, generously supplied by Eli Lilly and Company, through the courtesy of Dr. G. F. Kempf, Indianapolis City Hospital.

Control cultures were also made of the nonirradiated suspensions. The tubes were sealed with melted paraffin and incubated at 37°C. They were examined weekly with a hand lens and records were made of the time when growth appeared, of the number of tubes showing growth and of the approximate number of colonies per tube. Final recordings of failure of growth were made only after eight or more weeks' incubation.

*Tests of virulence of irradiated suspensions:* These were made by inoculating irradiated and control (nonirradiated) suspensions intracerebrally. Two normal animals were used to test each suspension. The dose of organisms was 0.01 mg. or larger. (This dose of virulent organisms introduced intracerebrally usually causes death in about three weeks.) Organisms were considered nonvirulent only when both animals inoculated remained symptom free for six weeks or longer.

*Tests of immunization:* Two varieties of such tests were made. First, animals which survived the intracerebral injection of a single dose of irradiated organisms (0.01 mg.) and remained well for six or more weeks were reinoculated intracerebrally, together with comparable normal controls, with a small dose of virulent organisms. Second, groups of guinea pigs which had been vaccinated subcutaneously with irradiated organisms, together with normal controls of comparable age, sex and weight, were inoculated intracerebrally with 0.000,01 mg. each of the homologous virulent strain of organisms. In such experiments the results were measured by longevity following virulent inoculation, and the significance of the result was determined by standard methods (20).

#### EFFECT OF IRRADIATION ON VIABILITY OF TUBERCLE BACILLI

Four separate suspensions of three different densities of human tubercle bacilli, strain H37, were irradiated with the mercury resonance lamp and samples were withdrawn at the intervals shown in table 1. Two to 5 tubes of glycerolated egg-yolk medium were seeded with each sample, sealed and incubated. The final result of the tests is shown in table 1.

It will be noted from the data that, with the least dense suspension (0.05 mg. per cc.), no growth was obtained in any of 60 tubes seeded with irradiated organisms, but the nonirradiated organisms grew massively. The organisms were apparently rendered nonviable by as little as one minute's exposure to the lamp. The suspension of inter-

mediate density (0.1 mg per cc) contained a very few viable bacteria after two minutes' exposure to the radiation. One of 2 tubes seeded with this sample showed a single colony, the duplicate tube was negative. However, with a suspension containing 1.0 mg of organisms per cc, there were still viable organisms after nine minutes' irradiation, while cultures of the ten-minute sample remained negative. This latter confirmed the observation made many years ago by Henri-Cernovodeanu, Henri and Baroni (21). The fact remains unexplained that the three-

TABLE 1

*Growth of human tubercle bacilli strain H37 after irradiation for various lengths of time*

IRRADIATION  minutes	DENSITY OF SUSPENSIONS EXPRESSED AS MG PER CC			
	0.05†	0.1	1.0	1.0
Control 0	5/5*	2/2	2/2	5/5
0.5		1/2	2/2	
1.0	0/5	0/2		5/5
1.5		0/2		
2.0	0/5	1/2		5/5
2.5			2/2	
3.0	0/5			0/5
4.0	0/5			1/5
5.0	0/5			2/5
6.0	0/5			5/5
7.0	0/5			5/5
8.0	0/5			2/5
9.0	0/5			5/5
10.0	0/5			0/5
12.5	0/5			
15.0	0/5			

\* Numerator = number of tubes showing growth. Denominator = number of tubes planted.

† This suspension was cleared of clumps by light centrifugation, then brought to desired density by comparison of turbidity with a standard suspension.

minute sample yielded no growth, and that there were negative tubes from the four- and five-minute samples of this suspension, while all tubes seeded from the six- and seven-minute samples showed growth. It must be remarked, however, that none of the irradiated samples yielded growth equal in quantity to the control nonirradiated samples, and in general it was true that samples irradiated successively longer showed progressively fewer colonies.

Smears of the irradiated bacteria were prepared and stained by the

Cooper method All the samples shown in table 1 retained their acid-fastness and could not be differentiated in the smears from the control nonirradiated organisms This observation is contrary to that of Cernovodeanu and Henri (22)

This result indicated that the radiation emitted by the lamp used was capable of quickly rendering tubercle bacilli nonviable when the suspensions were relatively weak, and showed that with more dense suspensions the time required to render the organisms nonviable was considerably prolonged Furthermore, very short exposure to radiation was effective in reducing the number of viable organisms, but longer exposure was necessary to kill them all

#### EFFECT OF IRRADIATION ON VIRULENCE

Three experiments were done to test the virulence of organisms exposed to radiation for varying lengths of time The nonirradiated and irradiated samples of each suspension were inoculated intracerebrally, each sample into 2 normal albino guinea pigs Relatively large doses were injected (not less than 0.01 mg) in order to be able to detect the presence of small numbers of virulent organisms which might survive the irradiation The H37 strain used in two of these experiments was fully virulent, the Lockett strain slightly less so From prior experience it was known that 0.01 mg of fully virulent organisms ordinarily causes death within about three weeks after intracerebral inoculation, and 0.000,001 mg usually causes death in less than six weeks (19) The experiments were therefore not terminated until six or more weeks after inoculation Table 2 shows the results of the experiment

The results shown in table 2 indicated that the Lockett organisms in suspension containing 0.1 mg per cc were nonvirulent after two minutes' exposure to the lamp These animals were observed for sixty-seven days and none showed any ill effects from the inoculations, the control animals inoculated with nonirradiated organisms both succumbed The middle vertical column in table 2 shows that a similar suspension of the H37 strain was rendered less virulent (the animals living longer than those inoculated with the nonirradiated suspension) by as little as fifteen seconds' exposure to the radiation, and nonvirulent by thirty seconds' exposure This was the same experiment as that in which a single colony was obtained in 1 of 2 tubes seeded with suspension irradiated two minutes (table 1) The result, therefore, indicated that although viable organisms were present they had either lost their viru-

lence or else were present in such small numbers as to allow survival without evidence of illness for forty-two days after inoculation. The experiment in the last column to the right in table 2 showed that in a heavier suspension of the H37 strain virulent organisms remained after two and one-half minutes' irradiation. This confirmed the result obtained by cultural methods (table 1) and showed that greater exposure to radiation is required for dense suspensions in order to reduce the virulence of the organisms or the number which are viable.

TABLE 2

*Virulence of human tubercle bacilli after irradiation, as determined by survival or death following intracerebral inoculation*

IRRADIATION	LOCKETT STRAIN 0.01 MG *	H37 STRAIN 0.01 MG	H37 STRAIN 0.1 MG
<i>minutes</i>			
0 25		D 36† D 31	
0 5		S	D 27 D 44
0 75		S	
1 0		S	
1 25		S	
1 5		S	
1 75		S	
2 0	S	S	
2 5			D 29 D 36
4 0		S	
6 0	S		
10 0	S		
14	S		
Control } 0 }	D 30 D 31	D 23 D 24	

\* This dose was inoculated in 0.1 cc. saline. The suspension irradiated therefore contained ten times this quantity per 1 cc.

† D indicates death on day shown. S indicates survival of both animals inoculated with a sample.

In summary of the tests of virulence we may say that an unknown number of organisms remained viable and virulent after two and one-half minutes' irradiation of a suspension containing 1.0 mg. of organisms per cc. When the suspension contained only 0.1 mg. of organisms per cc., fifteen seconds' exposure was adequate to appreciably reduce the virulence of the organisms (either by attenuation or by killing off a portion of them) and thirty seconds of exposure to the lamp rendered the organisms nonvirulent.

## TESTS OF IMMUNITY AFTER INJECTION OF IRRADIATED ORGANISMS

Each of the animals (table 2) which survived the intracerebral inoculation of 0.01 mg of either the irradiated Lockett or the irradiated H37 organisms was reinoculated intracerebrally with 0.000,01 mg of the homologous virulent organisms to ascertain whether the small quantity of organisms made nonvirulent by irradiation had induced measurable immunity. Normal control guinea pigs were inoculated at the same time with the same dose of organisms. All these animals succumbed to tuberculosis, and none of those first inoculated with irradiated organisms were more resistant to the test inoculation than the normal controls. This result indicated that no appreciable immunity is induced by a single intracerebral injection of 0.01 mg of irradiated tubercle bacilli.

Two additional experiments were done to determine whether enhanced resistance could be induced by subcutaneous injection of larger numbers of irradiated organisms. In both experiments the suspension irradiated contained 1.0 mg per cc of the strain H37. In the first experiment two irradiated samples were used as vaccine: one had been exposed to the lamp thirty seconds and the other two and one-half minutes. Both these specimens were found to contain a residuum of viable, virulent organisms (tables 1 and 2). In the second experiment two samples of vaccine were also used. One had been exposed to radiation for five minutes, the other for ten minutes. The five-minute sample was found to contain a few viable organisms (table 1) the virulence of which was not tested. Bacteriological tests indicated that the sample irradiated ten minutes contained no viable organisms. Each of the four irradiated samples of mycobacteria was injected subcutaneously daily for five days in each of a group of 5 or 8 normal guinea pigs. The daily dose for each animal was 0.3 mg. Eleven or fifteen days following the final injections of vaccine, these guinea pigs and comparable groups of non-vaccinated control animals were inoculated intracerebrally with 0.000,01 mg of the homologous virulent organisms to test their resistance. None of the animals was submitted to other experimental procedure. The criterion of resistance was the length of survival following test inoculation. The results of the experiments are shown in table 3.

The data in table 3 indicate that the animals vaccinated with organisms irradiated for one-half or two and one-half minutes were partially protected against virulent inoculation. Not only was the mean survival significantly prolonged in both these groups, but one animal of the group vaccinated with organisms irradiated two and one-half minutes survived the virulent inoculation and showed no ill effects thereof.

seventy-five days later. In the groups vaccinated with organisms irradiated five minutes and ten minutes, the mean survival was not significantly prolonged, but one animal survived in the group vaccinated with organisms irradiated five minutes. This result was considered

TABLE 3

*Survival time in days following intracerebral inoculation of 0.000,01 mg of virulent tubercle bacilli strain H37. Comparison of nonvaccinated controls with animals vaccinated with irradiated H37*

VACCINATED WITH H37 IRRADIATION	SURVIVAL IN DAYS		VACCINATED WITH H37 IRRADIATION	SURVIVAL IN DAYS	
	Individual	Mean		Individual	Mean
minutes			minutes		
0.5	35	53.3 ± 3.5	5	30	44.0 ± 3.4
	37			37	
	41			39	
	53			51	
	58			59*	
	60				
	67				
	75†				
2.5	47	63.3 ± 2.6	10	†	44.75 ± 3.8
	55			32	
	56			43	
	58			49	
	69			59‡	
	72				
	75‡				
	75*				
Nonvaccinated controls	22	33.0 ± 1.9	Nonvaccinated controls	28	40.4 ± 2.6
	26			37	
	28			42	
	29			45	
	36			50	
	39				
	42				
	42				

\* Animal in excellent condition. Sacrificed to end experiment.

† Animal succumbed to intercurrent infection.

‡ Animal paralyzed. Sacrificed.

significant because normal, nonvaccinated animals subjected to intracerebral inoculation of 0.000,01 mg of this line of the strain H37 inevitably succumbed.

From experiments reported earlier in this paper (table 1) we know that the vaccines irradiated respectively one-half, two and one-half and five

minutes contained viable organisms, while the suspension irradiated ten minutes apparently contained none. Thus the three groups of animals which showed demonstrable protection were vaccinated with suspensions which contained viable organisms, and the group which exhibited no protection was vaccinated with a suspension containing no viable organisms. This result would seem to indicate that the radiation rendered the organisms nonviable and inactivated the immunizing capacity at about the same time. However, it is possible that one might irradiate a less dense suspension for a shorter period and render the organisms nonviable while maintaining the immunizing power.

Microscopical surveys of the lesions in the three groups of animals in the left half of table 3 revealed that the preparatory vaccinations influenced the histogenesis of lesions. Pulmonary tubercles were not found microscopically in any of the 8 controls, but there were lesions in the tracheobronchial lymph nodes of all save one. Each control exhibited extensive lesions in the spleen, liver and cervical lymph nodes, and massive, acute tuberculous meningo-encephalitis. The lesions of the spleen and brain showed many tubercle bacilli. In the vaccinated groups, on the other hand, the lesions in brain and meninges were considerably less extensive (sometimes minimal), more of the hard type of tubercle and contained fewer organisms. We have previously described and illustrated similar lesions in animals vaccinated by other methods (23). Lesions in cervical nodes of the vaccinated groups were also less extensive. But lesions in other viscera such as spleen and liver were as extensive as in the controls. Moreover, the vaccinated animals in a few instances exhibited pulmonary lesions, possibly due to the fact that they survived longer.

Thus the vaccinations with irradiated suspensions containing viable bacteria afforded partial protection, as expressed by significantly greater survival and by complete protection of a small number of animals, and vaccination also exerted an inhibitory influence on the evolution of the local cerebral and meningeal lesions, but exerted no favorable influence on the development of metastatic lesions. (It is possible that a part of the visceral lesions in the vaccinated animals may have been caused by the vaccinations.) An irradiated suspension which contained no viable organisms gave no evidence of protection against virulent inoculation.

#### DISCUSSION

The significant points brought out by this investigation are first, that ultraviolet radiation may be so applied to tubercle bacilli that they are



rendered nonvirulent without being made nonviable, and second, that irradiated viable tubercle bacilli may induce demonstrable immunity in experimental animals

Regarding the first point we believe that the reduction in virulence is probably an effect on the individual bacterial cell which precedes the lethal effect occurring with prolonged exposure to radiation. The only other apparent explanation of the effect would be to assume that the reduction in virulence is due to early death, during irradiation, of a large proportion of the bacterial population, but that the survivors are virulent. The results show that early death of a portion of the bacteria does occur, but the methods used to study virulence are so sensitive, and the dose of organisms used to test the virulence of irradiated suspensions was so large, that death would certainly have occurred had virulent organisms been present in the inocula. However, suspensions which failed to cause death when inoculated intracerebrally still contained organisms which grew in culture.

This latter point may have a bearing on the view held by some workers that bacteriological methods are superior to animal inoculations for detecting tubercle bacilli. It is possible that their opinions are based on obtaining in culture attenuated organisms which are incapable of inducing disease in animals.

Regarding immunization with viable irradiated organisms it must be emphasized that this procedure is not recommended for practical purposes as it would undoubtedly be associated with unwarranted hazards. In our experiments, organisms killed by irradiation did not induce demonstrable immunity. However, we used in these experiments dense suspensions which required long exposure to the lamp (ten minutes) to render the organisms nonviable. The heavy suspensions were used because we desired to have a given quantity of organisms in the irradiated suspension to be used as vaccine. This result could be accomplished by other methods, and the possibility remains that a weak suspension might be used in which very short exposure to radiation would cause death of the bacteria, conceivably without denaturing or rendering ineffective the immunizing antigen.

#### SUMMARY

The effect of approximately monochromatic ultraviolet radiation (2,537 Å) upon saline suspensions of human tubercle bacilli has been studied. The following effects on the viability, staining properties, virulence and immunizing power were observed:

Heavy suspensions of tubercle bacilli (1 mg per cc) require relatively long periods of irradiation (ten minutes or more) to be rendered nonviable. Weaker suspensions are killed in shorter time.

Organisms killed by ultraviolet radiation retain the property of acid-fastness.

Heavy suspensions of tubercle bacilli are rendered avirulent only after relatively long exposure to ultraviolet radiation, but weak suspensions are quickly reduced in virulence. Reduction in virulence can be demonstrated after less irradiation than is required to kill the organisms, and organisms may be made avirulent without being killed.

Irradiated viable organisms possessed the capacity of inducing demonstrable immunity. Organisms killed by the radiation did not induce measurable immunity.

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## VITAMIN C AND IMMUNITY IN TUBERCULOSIS OF GUINEA PIGS<sup>1</sup>

FRED H. HEISE AND WILLIAM STEENKEN, JR.

An abundance of vitamin C fed to guinea pigs before and after infection with large numbers of virulent tubercle bacilli did not influence the course of the disease. It was thought that, when the infecting dose was smaller, some effect might be noticed. In the previous experiments 300,000 bacilli were given subcutaneously, in the following experiments 10,000 bacilli were given by the same route. In these experiments, too, the effect of vitamin C was studied in vaccinated and nonvaccinated guinea pigs.

One hundred tuberculin-negative albino guinea pigs were divided into four groups of 25, each group contained the same number of males and females. Two groups were vaccinated subcutaneously with a forty-day old resistant variant dissociate of H37 tubercle bacilli. Three doses of 2.5 mg. each were given on alternate days. All 50 of the guinea pigs reacted to 5 per cent OT intracutaneously two weeks later. Twenty-five vaccinated and 25 nonvaccinated pigs were then given daily 22 mg. of partially neutralized crystalline Cebione subcutaneously. At the end of two weeks the 50 pigs were infected subcutaneously with 10,000 tubercle bacilli of H37 *Rv* variant. The vitamin C was continued daily throughout the ten months of the experiment.

Twenty-five vaccinated and 25 nonvaccinated guinea pigs were likewise infected with H37 *Rv* variant but these groups had not received nor were they given any Cebione.

Intercurrent disease caused the death of 18 pigs, 4 in the Cebione control, 2 in the Cebione, 7 in the Cebione-vaccinated and 5 in the vaccinated group. Six pigs died of tuberculosis before the termination of the experiment. All were in the nonvaccinated groups. Two were in the Cebione control and 4 in the Cebione group. At the end of ten months there remained alive in the nonvaccinated groups 19 in the Cebione control and 19 in the Cebione group. In the vaccinated groups 18 remained in the Cebione and 20 in the non-Cebione group.

<sup>1</sup> From Trudeau Research and Clinical Laboratory, Trudeau, New York.

All living guinea pigs were then killed and autopsied. In the non-vaccinated group as in the vaccinated group no major differences could be seen in the amount and character of the tuberculosis between those pigs receiving vitamin C and those not receiving it. There was a marked difference, however, in the development of tuberculosis in the vaccinated as compared to the nonvaccinated pigs. The vaccinated pigs showed marked resistance in that the amount of tuberculosis in the lungs, liver, spleen and lymph nodes was only a fourth or less of that found in the nonvaccinated pigs.

Vitamin C determinations were made on the blood sera of 5 animals from each of the four groups. No marked differences were noted in any group. Variations occurred from 0.88 mg per cent to 1.66 mg per cent.

Sixteen animals not receiving Cebione and 15 which did receive it were tested intracutaneously for tuberculin sensitivity with 0.1, 0.5, 1.0 and 2.0 per cent OT. No marked difference in skin sensitivity was noted between the groups.

Rotter's (2) intracutaneous test for vitamin C was tried in the controls and Cebione group. In the Cebione group decolorization did not take place sooner than in the controls.

During the experiment one of the tuberculous control pigs gave birth to three babies. These were left in contact with their mother. The three did not react to OT intracutaneously one month after birth. At the end of three months one developed skin hypersensitivity and later died. H37 Rv bacilli were recovered at autopsy.

#### CONCLUSIONS

Vitamin C given subcutaneously and in abundance

- 1 Does not influence the course of tuberculosis in guinea pigs infected with 10,000 H37 Rv bacilli,
  - 2 Does not influence the vitamin C blood serum content,
  - 3 Does not influence tuberculin sensitivity in tuberculous guinea pigs.
- Rotter's test proved of no value in differentiating supervitaminosis C.

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## **PATHOLOGICAL CHANGES IN PULMONARY TUBERCULOSIS IN JAMAICAN NEGROES<sup>1</sup>**

C W WELLS

Studies of tuberculosis conducted in Jamaica, British West Indies, during the past nine years have included postmortem examinations of patients dying with pulmonary tuberculosis. This report gives the pathological findings in 113 autopsies of Jamaican Negroes, performed as opportunity and permission could be obtained. The majority of the cases were on the register of the Kingston Tuberculosis Dispensary and, with one exception, all of the patients died while inmates of the local Alms House. For those who did not pass through the Tuberculosis Dispensary a clinical history was unobtainable.

The cases included in this study were all Negroes, comprising 58 males and 55 females, the majority were over eleven and under fifty years of age, the average being 28.9 years.

Adult and childhood types of progressive pulmonary tuberculosis may often be differentiated by X-ray, but in many instances such examinations are inconclusive. Autopsy findings, especially when supplemented by X-ray films of the excised lung, usually provide sufficient evidence to catalogue properly the type of disease. In this study the freshly excised lung was routinely X-rayed, in many instances after being inflated. Such examinations often revealed small calcified pulmonary nodules which otherwise might have escaped notice. The criteria employed in this paper for the differentiation of childhood from adult progressive pulmonary tuberculosis have been taken from the Diagnostic Standards published by the National Tuberculosis Association (1) and from Opie (2). Cases have been classified as childhood tuberculosis when caseous tracheobronchial lymph nodes were demonstrated, associated with tuberculous disease in the lung tissue. This condition occurred in 27 instances. In 6 additional cases the tracheobronchial lymph nodes were greatly enlarged and hyperplastic, but

<sup>1</sup> This study was conducted with the support and under the auspices of the International Health Division of The Rockefeller Foundation, in cooperation with the Jamaica Government Medical Department.

grossly no caseation was apparent, these are also included in the group of childhood type of tuberculosis. In 4 other cases definite caseation was found in the tracheobronchial lymph nodes, associated with calcified nodules in the lung substance, these also are classed as childhood tuberculosis, making a total of 37 cases (32.7 per cent) of the entire series.

Adult type pulmonary tuberculosis has been determined in 51 instances by the presence of calcified pulmonary nodules or calcified tracheobronchial lymph nodes, associated with active disease in the lung and an absence of acute involvement in the lymph nodes. In 25 additional cases classed as adult type tuberculosis careful examination, which included routine X-ray of the fresh lung and dissection after fixation, failed to disclose the presence of calcified lesions either in the lymph nodes or lung tissue. In this group, likewise, there was an absence of caseous involvement of the lymph nodes. A total of 76 (67.3 per cent) of the

TABLE 1

*Average age, duration of disease and length of residence in Kingston*

	CHILDHOOD TYPE PULMONARY TUBERCULOSIS		ADULT TYPE PULMONARY TUBERCULOSIS	
	Number of cases	Average	Number of cases	Average
Average age of all cases	37	21.5 yrs	76	32.4 yrs
Average age of individuals over 15 years	31	24.2 yrs	75	32.7 yrs
Average duration of illness	28	8.5 mos	66	15.3 mos
Average length of residence in Kingston	25	8.6 yrs	61	15.6 yrs

cases in this series have been classified as adult progressive pulmonary tuberculosis.

#### CHILDHOOD TYPE PROGRESSIVE PULMONARY TUBERCULOSIS

Thirty-seven of the 113 cases have been classified as childhood type pulmonary tuberculosis. These persons varied in age from nine months to forty-seven years (table 6), the average being 21.5 years. For those over fifteen years of age the average was 24.2 years. The length of illness was determined in 28 of these cases and averaged 8.5 months. The average length of residence in Kingston for 25 cases was found to be 8.6 years (table 1). The occurrence of hilar lymph node involvement and of pleural effusions and adhesions is presented in tables 2 and 6.

In 3 instances the disease was miliary in character, these were in

children nine months, twenty-two months and six years of age, respectively. In one of these children and in the remaining 34 cases it was possible to determine the site of the primary disease. The primary lesions were distributed in frequency as follows: right lower lobe, 5, right middle lobe, 2, right upper lobe, 12, left lower lobe, 7, left upper lobe, 9. The primary lesion occurred most frequently on the right side.

TABLE 2  
*Occurrence of pleural involvement in 113 autopsies*

TYPE	TOTAL NUMBER OF CASES	PERCENTAGE OF TOTAL CASES	PLEURISIA WITH EFFUSION					PLEURISIA WITH ADHESIONS												
			Right side	Left side	Bilateral	Total	Per cent	Unilateral		Bilateral	Total	Per cent	Complete obliteration				Fibrous	Fibrous	Both fibrous and fibrous	Total
								Right side	Left side				Right side	Left side	Bilateral	Total				
Childhood	37	32.7	5	3	0	8	21.6	11	12	13	36	97.3	3	8	0	11	11	20	5	36
Adult	76	67.3	6	12	1	19	25.0	10	14	51	75	98.7	13	6	6	25	1	71	3	75

TABLE 3  
*Distribution and character of lung involvement*

TYPE	LOCATION OF PRIMARY OR MAJOR PULMONARY LESIONS						CHARACTER OF LUNG INVOLVEMENT			AVERAGE DURATION OF ILLNESS (IN MONTHS) IN RELATION TO CHARACTER OF LUNG INVOLVEMENT			PULMONARY CAVITIES										
													Location				Per cent with cavities	Character of cavity walls			Duration of illness (in months) in relation to walls of cavities		
	Right upper	Right middle	Right lower	Left upper	Left lower	Total	Caseous	Fibrotic	Fibrocascous	Caseous	Fibrotic	Fibrocascous	Right lung	Left lung	Bilateral	None	Thick smooth	Thin smooth	Necrotic irregular	Thick	Thin	Necrotic	
Child hood	12	2	5	9	7	35	27	1	7	6.4	?	15.4	8	10	11	8	18.4	9	8	13	12.4	12.3	7.3
Adult	37	0	1	38	0	76	9	32	35	5.1	18.7	14.7	20	15	39	2	97.4	43	28	10	16.7	17.6	9.3

and 21 times in upper lobes compared to 14 times in the middle or lower lobes (tables 3 and 6).

The distribution of cavities and the character of their walls are shown in table 6.

As might be expected, both from the type of the disease and its short duration, the character of the lung involvement in these cases of childhood tuberculosis was predominantly caseous infiltration, either bron-

chopneumonic or confluent This type of involvement was found in 34 of the 37 cases in the series On the other hand, fibrous tissue formation was not entirely absent, but was found in only 8 cases in this series, in conjunction, however, with caseous involvement In 1 case the reaction in the lung tissue was almost exclusively fibrotic In 6 of the cases in which fibrous tissue occurred the disease had progressed for more than one year.

The secondary involvement of other organs and tissues is not infrequent in pulmonary tuberculosis, in this group of 37 cases of childhood tuberculosis, lesions were found in other organs in 21 cases, the most

TABLE 1  
*Distribution of secondary lesions*

TYPE	PERI CARDIUM		PERI TONICUM		MESENTERIC LYMPH NODES		INTESTINES		SPLEEN		LIVER		KIDNEYS		TRACHEA		TOTAL NUMBER CASES
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	
Childhood	2	5.4	9	24.3	15	40.5	6	16.2	11	29.7	6	16.2	1	2.7	1	2.7	37
Adult	12	15.8	7	9.2	9	11.8	10	13.2	4	5.3	6	7.9	0	—	2	2.6	76

TABLE 5  
*The proportion of cases of manifest tuberculosis of childhood type according to age at death*

AGE AT DEATH (ALL CASES)	TOTAL NUMBER OF CASES	NUMBER WITH CHILDHOOD TYPE	PER CENT WITH CHILDHOOD TYPE
0-14	7	6	86
15-24	39	17	44
25-30	49	13	27
40+	18	1	6

frequent finding being caseation of the mesenteric lymph nodes, tubercle formation in the spleen, and tuberculous peritonitis Less frequently, secondary lesions were found in the intestines as ulcers, as tubercles in the liver and kidney, tuberculous pericarditis, and ulceration of the trachea (tables 4 and 6)

#### ADULT TYPE PULMONARY TUBERCULOSIS

Seventy-six cases (67.3 per cent) of the entire series have been diagnosed as adult type pulmonary tuberculosis Twenty-five of these cases deserve special comment, for the reason that no evidence of calci-



TABLE 6  
Childhood type pulmonary tuberculosis

TABLE 6  
Childhood type pulmonary tuberculosis

CASE NUMBER	AGE	SEX	COLOR	LENGTH OF ILLNESS	LENGTH OF RESIDENCE IN KINGSTON	TRACHEO BRONCHIAL LYMPH NODES		CALCIFIED PULMONARY NODULES	PLEURAL INVOLVEMENT		LUNG INVOLVEMENT				CAVITIES		SECONDARY TUBERCULOUS LESIONS IN																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																				
						Caseous	Hypertrophic		Effusion	Adhesions*	Site of primary lesion	Caseous pneumonia	Fibrosis	Miliary	Site**	Character of walls	Pericardium	Mesenteric lymph nodes	Intestines	Spleen	Liver	Kidneys	Trachea																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
1	9 mo	F	DB	5 mo	9 mo	+				L	?	+		+				+	+	+	+																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																



TABLE 6—Concluded

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CASE NUMBER	AGE	SEX	COLOR	LENGTH OF ILLNESS	LENGTH OF RESIDENCE IN KINGSTON	TRACHEO BRONCHIAL LYMPH NODES		CALCIFIED PULMONARY NODULES		PLEURAL INVOLVEMENT		LUNG INVOLVEMENT				CAVITIES		SECONDARY TUBERCULOUS LESIONS IN										
						Casous	Hypertrophic			Effusion	Adhesions*	Site of primary lesion	Casous pneumonia	Fibrosis	Miliary	Site**	Character of walls	Pericardium	Mesenteric lymph nodes	Intestines	Spleen	Liver	Kidneys	Trachea				
22	29 yr	M	DB	1 yr 3 mo	?	+					L-C R	LU	+	+		LU	Thin		+	+	+	+						
23	34 yr	F	B	1 yr	11 yr	+					R L	RU	+	+		RU LU	Thick Thin	+		+								
24	37 yr	M	B	?	37 yr	+					R-C-F	RU	+			RU	Necrotic			+								
25	47 yr	M	B	6 mo	4 yr	+					L-C	LU	+			LU LL	Necrotic Necrotic											
26	26 yr	M	B	?	?	+					R	LL		+														
27	16 yr	F	DB	5 mo	16 yr	+					L	LL	+			LL	Thin	+		+								
28	18 yr	F	B	1 yr 4 mo	3 mo		+				L	LL	+			LL	Thick											
29	18 yr	F	DB	?	?	+					R-C L-F	RL	+															
30	22 yr	M	DB	?	?	+					L R	LL	+			LL RU	Thin Thin		+	+								
31	25 yr	F	DB	6 mo	1 yr	+					R	RU	+			RU LU	Necrotic Necrotic											

802

32	16 yr	M	DB	4 mo	16 yr		+		100 cc L	L-F	LU	+		LU RU	Thick Necrotic		+	+	
33	33 yr	M	B	9 mo	?		+			R	RU	+		RU LU	Thick Thin				
34	15 yr	F	B	2 yr 6 mo	5 yr	+		+		R L	RU	+	+	RU LU	Thick Thin				
35	25 yr	M	DB	8 mo	6 yr	+		+		R L-F	LU	+		LU LL RU	Thick Thick Necrotic		+	+	
36	30 yr	M	B	1 yr 6 mo	7 yr	+		+		L-C	LU	+	+	LU	Thick				
37	31 yr	M	DB	?	?	+		+		R-F	RU	+		RU RL	Necrotic Necrotic				

\* F = Fibrinous exudate and adhesions easily separated

C = Complete obliterative pleuritis

\*\* First lobe mentioned constitutes site of largest cavity

fied lesions could be detected in the tracheobronchial lymph nodes or lung tissue (table 7a), there was, however, an absence of caseation or hyperplasia of the lymph nodes. The average age for this special group of 25 cases was 32.2 years, the average duration of illness 14.9 months, the average length of residence in Kingston 14.7 years. The remaining 51 cases presented the classical features of adult type pulmonary tuberculosis associated with lung involvement, either calcified tracheobronchial lymph nodes, in 4 instances, or calcified pulmonary nodules, in 27 instances, or both in combination, in 20 instances (table 7b). The average age for this group of 51 cases was 32.5 years, the average duration of illness 15.5 months, the average length of residence in Kingston 16.1 years. For the entire group of 76 cases of adult type pulmonary tuberculosis (table 1) the average age was 32.4 years, average duration of illness 15.3 months, average length of residence in Kingston 15.6 years.

The type and distribution of pleural involvement are shown in tables 2, 7a and 7b.

By definition, adult type pulmonary tuberculosis characteristically arises in one of the upper lobes, in the majority of instances. In this series the disease appeared to originate in the right upper lobe 37 times, the left upper lobe 38 times, and once in the right lower lobe. In the last case there were found definite calcified pulmonary nodules in the right lower lobe and a small calcified mesenteric lymph node near the caecum.

Cavities were found in 74 of the 76 cases of adult type pulmonary tuberculosis, the cavities were of a considerable size. Single cavities occurred in 26 instances, in 9 cases multiple cavities were confined to one side and in 39 instances they were bilateral (tables 3, 7a and 7b).

As would be expected in the more chronic type of pulmonary tuberculosis, in the majority of cases the walls of these cavities showed more extensive organization, thick fibrotic walls were found in 43 instances, thin, smooth walls in 28 instances, and rough, irregular, necrotic walls in 10 instances. There was also found a definite association between the degree of organization of the cavity walls and the duration of the disease. The average duration of the disease in patients with thick walls was 16.7 months, thin walls, 17.6 months, and irregular necrotic walls, 9.3 months.

The character of the pulmonary involvement in tuberculosis is usually influenced by the chronicity of the disease. In this series of adult type

pulmonary tuberculosis, fibrous tissue formation predominated in 32 instances, fibrosis, associated with caseous infiltration, was found in 35 instances, and in 9 instances the pulmonary lesions were almost exclusively caseous. The type of infiltration may also have a relation to the duration of the disease, in cases with chronic caseating lesions, this was found to be 5.1 months, in cases with involvement of the fibrocaseous type, 14.7 months, and in cases in which the local tissue reaction was predominantly fibrous tissue formation, 18.7 months (table 3).

Secondary involvement of other organs was not particularly striking in this series of adult type pulmonary tuberculosis. The frequency of such distributions is shown in table 4.

In none of the cases in this study of 113 autopsies was an attempt made to determine the occurrence of cerebral-spinal lesions.

#### DISCUSSION

This paper reports the character of tuberculous lesions found at autopsy in 113 Negroes dying of pulmonary tuberculosis in Jamaica, British West Indies. The acute character, as well as the short duration of pulmonary tuberculosis, has been reported by Opie and Isaacs (3). Also, the anatomical characteristics of tuberculosis in Jamaica have been described by Opie (2) in a review of 9 cases among adults. These reports manifest the frequent occurrence among Negroes of a type of progressive pulmonary tuberculosis designated as childhood type.

The frequency of childhood type pulmonary tuberculosis is determined by the opportunities for first infection of a massive character by persons lacking protection through previous exposure and infection. Such conditions are prevalent in Jamaica. The exposure rate to active and infectious tuberculosis in the rural parts of Jamaica is considerably lower than that found in Kingston. Many noninfected young adults migrate from the country to the city in search of employment and, for economic reasons, live in those sections where the highest frequency of tuberculosis occurs. Economic and living conditions not only influence the type of disease but also undoubtedly affect its course.

This series of 113 autopsies includes 37 classified as progressive pulmonary tuberculosis of childhood type, 32.7 per cent of the entire series. A review of 1,032 cases of pulmonary tuberculosis in Negroes observed at the Kingston Tuberculosis Dispensary during 1931 to 1934 showed 28.9 per cent diagnosed as clinical childhood type tuberculosis. In practically all of these cases the diagnosis was determined by X-ray

TABLE 7A  
Adult type pulmonary tuberculosis among persons with no demonstrable lesions of childhood type

CASE NUMBER	AGE Year	COLOR	SEX	LENGTH OF ILLNESS	LENGTH OF RESIDENCE IN KINGSTON	CALCIFIED TRACHEO- BRONCHIAL TUBER- CLES	CALCIFIED PULMO- NARY NODULES	PLEURISY WITH EFFUSION	PLEURITIC ADHESIONS*	SITE OF MAJOR LUNG LESION	CASEOUS TUBERCU- LOUS PNEUMONIA	PULMONARY FIBROSIS	CAVITIES		SECONDARY TUBERCULOUS LESIONS †					
	Year				Years								Site**	Character of walls	Percardium	Peritonaeum	Mesenteric lymph nodes	Intestines	Spleen	Liver
38	15	B	F	8 mo	2				L R	RU	+		RU	Thin		2000 cc		+		
39	22	B	M	?	?				L	LU		+	LU	Thick Thick Thick			+			
40	23	DB	F	4 mo	3				R	RU	+		LU	Thin						+
41	24	DB	F	?	17				L	LU	+		LU	Thick Thin Thin			+			
42	24	B	M	1 yr 6 mo	9			2000 cc R	L-C	LU	+		LU	Thick Necrotic						
43	24	DB	M	2 yr 3 mo	12			150 cc R 250 cc L	L R	LU	+	+	LU	Thick Necrotic						
44	26	DB	F	5	1			50 cc L	R-C	RU	+	+	RU	Thin						
45	26	B	F	1 yr 9 mo	4				L R	LU			LU	Thick Thick	500 cc				+	
46	27	DB	F	1 yr	?			200 cc R	L R	LU	+	+	LU	Thick Thick	100 cc					
47	27	DB	F	6 mo	?			1500 cc L	L R	LU	+	+	LU	Thick						
48	28	DB	M	1 yr 9 mo	10				R-C L	RU	+	+	RU	Thick Thick Thick						





TABLE 7b  
Adult type pulmonary tuberculosis among persons with demonstrable lesions of childhood type

CASE NUMBER	AGE years	COLOR	SEX	LENGTH OF ILLNESS	LENGTH OF RESIDENCE IN KINGSTON	CALCIFIED TRACHEO BRONCHIAL LYMPH NODES	CALCIFIED PULMO NARY NODULES	PLEURISY WITH EFFUSION	PLEURITIC ADHESIONS*	SITE OF MAJOR LUNG LESION	CASEOUS TUBERCU LOUS PNEUMONIA	PULMONARY FIBROSIS	CAVITIES		SECONDARY TUBERCULOUS LESIONS*								
													Site**	Character of walls	Pericardium	Peritoneum	Mesenteric lymph nodes	Intestines	Spleen	Liver	Trachea		
63	12	B	F	3 mo	12 yr		+		R	RL	+	+	RL	Necrotic	100 cc								
64	16	B	M	7 mo	16 yr	+	+		R-C L	RU	+		RU LU	Thin Thin									
65	17	B	M	7 mo	11 yr	+	+		L R	LU	+	+	LU RU LL	Thick Thick Thick									
66	18	B	F	4 yr	17 yr	+		250 cc R	R	RU	+		RU LU	Thin Thin									
67	19	B	M	4 mo	15 yr	+	+		R-C	RU	+		RU	Necrotic									
68	19	B	M	7 mo	19 yr	+	++		L-C R	LU	+	+	LU RU	Thin Thin					+	+			
69	20	B	F	3 mo	5 yr		+		L R	LU	+		LU RU	Thin Thin									
70	20	B	F	5 mo	7 mo				R-F L-F	RU	+		LU RU	Thin Thin									
71	20	B	F	8 mo	1 yr	+	500 cc L		R-C L-C	LU			LU RU	Thin Thin									
72	21	B	M	8 mo	16 yr	+	1000 cc R		L-C	LU	+		LU RU	Thin Thin	75 cc		+	+	+				
73	22	B	M	9 mo	?	+		R L	RU	+			RU RL LU	Thin Thin Thin									

71	23	B	M	1 yr	7 yr	+	+		L	IU		I	IU	+	IU	+	Thick	100 cc	
75	21	B	I	6 mo	9 yr		+		I	IU		I	IU	+	IU	+	Thick		
76	21	B	I	3 mo	8 yr				I	IU		I	IU	+	IU	+	Thick		
77	21	DB	I	6 mo	6 yr				I	IU		I	IU	+	IU	+	Thick		
78	21	DB	M	3 yr 3 mo	1 yr				L-C	IU		I	IU	+	IU	+	Thick		
79	24	B	M	10 mo	5 yr				L	IU		L	IU	+	IU	+	Thick		
80	26	DB	I	2 yr 1 mo	8 yr				L	IU		L	IU	+	IU	+	Thick		
81	28	B	I	1 yr	13 yr 6 mo				I-C	IU		I	IU	+	IU	+	Thick		
82	28	B	M	?	?				R	IU		R	IU	+	IU	+	Thick		
83	28	DB	M	1 yr	28 yr				I	IU		I	IU	+	IU	+	Thick		
84	29	DB	M	2 yr 8 mo	10 yr				R	IU		R	IU	+	IU	+	Thick		
85	29	B	I	1 yr	11 yr				L	IU		L	IU	+	IU	+	Thick		
86	30	B	F	1 yr 1 mo	4 yr				L	IU		L	IU	+	IU	+	Thick		
87	30	DB	F	2 yr 2 mo	10 yr				R	IU		R	IU	+	IU	+	Thick		

\* I = Fibrous cavity and adhesions easily separated  
 C = Complete obliterative pleuritis  
 \*\* First lobe mentioned constitutes site of largest cavity

TABLE 7n—Concluded

CASE NUMBER	AGE	COLOR	SEX	LENGTH OF ILLNESS	LENGTH OF RESIDENCE IN KINGSTON	CALCIFIED TRACHEO-BRONCHIAL LYMPH NODES	CALCIFIED PULMONARY NODULES	PLEURISY WITH EFFUSION	PLEURITIC ADHESIONS*	SITE OF MAJOR TUBERCULOUS PNEUMONIA	CASEOUS TUBERCULOUS PNEUMONIA	PULMONARY FIBROSIS	CAVITIES		SECONDARY TUBERCULOUS LESIONS IN								
													Site**	Character of walls	Pericardium	Pleuroperitoneum	Mesenteric lymph nodes	Intestines	Spleen	Liver	Trachea		
88	30 years	B	F	11 mo	17 yr	+	+		R-C L-C	RU		+	RU LU	Thick Thick				+					
89	30	DB	M	1 mo	12 yr	+	+		L	LU	+	+	LU LL	Necrotic Necrotic							+		
90	31	B	M	6 yr	30 yr	+	++		L R	LU		+	LU RU	Thin Thin									
91	31	B	M	9 mo	25 yr		+	100 cc R	R L	RU	+	+	RU	Thick									
92	32	DB	M	?	?		+		L-F R	RU		+	RM RU LU	Thin Thin Thin									
93	32	DB	M	?	?	+	+		L	LU		+	LU	Thin									
94	31	DB	M	1 mo	?		+		L-C	LU	+	+	LU	Thin									
95	35	B	F	3 yr	?	+	+	2500 cc L	L R	RU	+	+	RU	Thick									
96	35	B	M	1 yr 3 mo	35 yr		+		R	RU		+	RU	Thin									
97	37	DB	F	1 yr 1 mo	11 yr	+	+		R-C L	RU	+	+	RU	Thick				+					
98	38	DB	M	?	?		+		L R	LU	+	+	LU RU	Thick Thin	+								
99	39	B	M	1 yr 4 mo	34 yr		+		L R	LU	+	+	LU RU	Thick Thick	+								

100	39	B	M	4 mo	39 yr		+	50 cc L	R-C L	LU	+	+	LU LL	Thick Thick	+				
101	40	B	Γ	11 mo	20 yr		+	200 cc L		RU		+	RU LU	Thick Thick					
102	40	DB	F	8 mo	4 yr		+	50 cc L	L R-C	RU		+	RU LU	Thick Thick					
103	40	DB	F	1 yr 2 mo	2 mo		+	100 cc L	L R	LU		+	LU	Thick		100 cc		+	+
104	44	B	M	1 yr 3 mo	?		+			L LU		+	LU	Thick					
105	45	B	M	1 yr 5 mo	45 yr		+		R-C L-C	RU		+	RU LU	Thick Necrotic					
106	47	DB	M	3 yr	47 yr		+		R-C L	RU		+	RU	Thick					
107	51	B	M	1 yr	21 yr		+		L R	LU		+	LU LL	Thin Necrotic					
108	54	B	M	7 mo	32 yr		+		L R-F	LU		+	LU	Thick					
109	54	DB	M	?	?		+		R L	LU		+	LU RU	Thick		1000 cc		+	+
110	55	DB	F	?	?		+		L R	RU		+	RU	Thin					
111	50	B	F	1 yr 2 mo	5 yr		+		L-C R-C	LU		+	LU RU	Thick Thick					
112	40	DB	M	6 mo	40 yr		+		R-C L	LU		+	LU RU	Thick Thick					
113	80	DB	M	?	?		+		R L	RU		+	RU LU	Thin Thin					

\* Γ = Fibrinous exudate and adhesions easily separated  
C = Complete obliterative pleuritis  
\*\* First lobe mentioned constitutes site of largest cavity

\* Γ = Fibrous exudate and adhesions easily separated  
C = Complete obliterative pleuritis  
\*\* First lobe mentioned constitutes site of largest cavity

examination The proportion of childhood type pulmonary tuberculosis in any group of patients will be influenced by many factors, even though that of race remains constant Whatever these factors may be, that of greatest importance is the opportunity which has occurred for previous infection and thus, naturally, will be less for persons who have recently come to the city These conditions held for many cases of tuberculosis encountered in Kingston

Complete clinical history could not be obtained in a certain proportion of cases in this series In those cases in which the information was available, rather interesting comparative data were obtained concerning childhood and adult types of pulmonary tuberculosis with respect to the average age at death Table 5 shows the distribution of cases of tuberculosis of childhood type by age groups at death The decrease in the proportion of cases of childhood type with advancing age is to be expected The interesting feature is the fact that these cases occurred so late in life

Duration of illness in the childhood type group varied from two months to two years and six months, with an average of 8.5 months, while for the adult group this varied from three months to six years, with an average of 15.3 months The findings in the former group are comparable with those reported by Opie (2) It is significant that 61 patients with adult type tuberculosis had lived in Kingston for an average of 15.6 years, thus offering greater opportunity for previous exposure to infection, and 19 cases classed as childhood type in persons over fifteen years of age had lived in the city an average of only 9.8 years It is probably not exceptional for a person living in a city to escape infection for years, although undoubtedly in the majority of instances this would not occur

The cases of childhood type pulmonary tuberculosis in this series include 4 having caseous tracheobronchial lymph nodes associated with small calcified pulmonary nodules, and 6 additional cases in which caseation in lymph nodes could not be detected microscopically although the nodes were several times normal size and definitely hyperplastic It is felt that these cases may be included in the childhood type group Opie (2) reports 2 cases in which the adjacent lymph nodes have undergone hyperplasia, with some inconspicuous caseation, these he has designated transitional types Both of these cases showed encapsulated caseous foci either in the lung substance or lymph nodes Opie suggests the possibility that these encapsulated lesions developed shortly before,

or perhaps simultaneously with, the progressive pulmonary disease that caused death. The same explanation might apply to the 10 cases in this series mentioned above.

The group of adult type pulmonary tuberculosis included 25 cases in which no calcified lesions could be discovered in the lymph nodes or lung tissue. In these cases there was an absence of caseation or hyperplasia of the lymph nodes. Calcified lesions may escape detection because of their small size or because they are obscured by dense superimposing or surrounding infiltrative processes in the lung. All of the cases in this group except one showed moderate to extensive cavitation. It is not improbable that in some instances excavation may involve that portion of lung which was the site of the primary infection, and that the loss of lung tissue might embrace the calcified lesion, thus accounting for its disappearance.

In Negroes of Philadelphia, Everett (4) found evidence of first infection (calcified lesion) in only 15 of 22 cases of adult type tuberculosis, a proportion practically identical with that obtained in this series.

Involvement of the pleura occurred in all but 2 of the 113 cases in the series. The character of the pleural involvement differed in some degree in relationship to the type of the pulmonary disease. In 16 (43.2 per cent) of the cases of childhood type tuberculosis the involvement was largely fibrinous, with or without fluid, compared to 5.3 per cent similar involvement in the cases of adult type tuberculosis. The significance of this difference is shown by  $\chi^2 = 24.6$ ,  $P = 0.000$ . This fibrinous type of reaction seemed to be related to the shorter duration of illness. In 13 cases of childhood type, where the information was available, the average length of illness was 6.2 months, and for 3 adult type cases, 11.7 months. On the other hand, dense fibrous adhesions occurred more frequently in adult type tuberculosis. Seventy-one (93.4 per cent) were of this type, compared to 20 (54.1 per cent) in the childhood type tuberculosis. That this difference is significant is further shown by  $\chi^2 = 24.6$ ,  $P = 0.000$ . Here again there was a relationship between the nature of the pleuritic involvement and the duration of illness. Childhood type tuberculosis with such pleuritic involvement averaged 11.1 months in duration of illness and the adult type cases 15.5 months.

Autopsy reports on findings in Negroes dying from pulmonary tuberculosis contain little with reference to the extent of pleural involvement. Pirie and Mavrogordato (5) report pleurisy occurring in 89 (36.9 per cent) of 241 thoracic type cases of tuberculosis in South African natives.

Everett (4) does not discuss the frequency of pleural involvement, but search through the protocols of his Negro cases discloses reference to pleuritic involvement in 50 per cent of adult type tuberculosis and in 13.6 per cent of his childhood type cases

A number of references to pleuritic involvement in white patients are available, the frequency varying from 42.4 per cent (6) in Glasgow to 100 per cent (7) in California. Opie (2) writes, "The well-known characteristics of pulmonary tuberculosis of young children are as follows. The lesion may have its origin in any part of the lung substance and is not more frequently situated in the apex than elsewhere in the later period of childhood and in adult life tuberculosis of white persons (*adult type*) assumes a different character. The lesion has its origin at the apex of the lung, progressive type of childhood usually pursues an acute course, there is in most instances little formation of fibrous tissue and cavity formation is much less common than in adults with progressive pulmonary tuberculosis of adults fibrosis and cavity formation are rarely absent." In the same reference Opie reports 8 cases, 6 childhood tuberculosis and 2 transitional forms, in 5 of which the disease had its origin in a lower lobe, in the remaining 3 cases the origin was in an upper lobe. Everett (4) reports pathological findings in 22 cases of childhood tuberculosis and an equal number of adult type tuberculosis in Negroes. In the childhood type the disease had its origin in an upper lobe in 13 instances, in the remaining 9 cases it originated in a lower lobe. In 35 cases of childhood type, 21 (60 per cent) occurred in an upper lobe, the remaining 14 occurred in one of the lower lobes. Two cases of miliary tuberculosis failed to show any evidence of the origin of the disease. In 76 cases of adult type, 75 arose in an upper lobe. These findings agree closely with the classical characteristics described above. In a large proportion of the cases of progressive tuberculosis of childhood type, caseous or fibrocaseous tissue reactions predominated in 34 out of 37 cases (91.9 per cent). In the adult type tuberculosis only 57.9 per cent showed similar reactions and in the latter group the fibrocaseous reaction predominated. The difference in the frequency of occurrence of this type of reaction between childhood and adult types is definitely significant,  $\chi^2 = 13.5$ ,  $P = 0.000$ . Fibrous tissue formation occurred seldom in the cases of childhood type tuberculosis—in this series, once. This type of tissue reaction, however, predominated in 32 instances in the adult group. Everett (4) found a

similar difference but a more frequent occurrence of fibrous tissue formation in his childhood group

According to Opie (2), cavity formation is much less common in the childhood type of tuberculosis. Everett reports that cavities were found in 18 of 22 cases of childhood type, and in every instance in 22 cases of adult type of the disease. In the present series cavities were found in 29 out of 37 cases of childhood type tuberculosis (78.4 per cent) and in 74 out of 76 cases of adult type (97.4 per cent). This difference is definitely significant,  $\chi^2 = 11.1$ ,  $P = 0.001$ . In the childhood group cavity formation occurred most frequently in an upper lobe (19 instances), and only 10 times in a lower lobe. On the other hand, in the adult type tuberculosis group the principal cavity formation occurred in an upper lobe in 72 of the 74 cases having cavities. The character of the wall formation of cavities differed somewhat in the two groups of cases. Thick organized, smooth-walled cavities predominated in the adult type tuberculosis group, while ragged, necrotic, caseous walls were more frequent in the childhood type tuberculosis group. In both groups there was a definite relationship between the duration of the disease and the character of the walls of the cavities, death occurring in a shorter time in those cases having necrotic and unorganized cavity walls.

The frequency of extrapulmonary lesions in tuberculosis in Negroes varies somewhat in the reports of other writers. Everett (4) has little to say concerning such lesions, but mentions the occurrence of tuberculous peritonitis in 5 of his 22 cases of childhood tuberculosis and once in 22 cases of adult tuberculosis. Harvey, Pirie and Mavrogordato (5) in 241 cases of thoracic type report the frequency of secondary tuberculous lesions in the following organs and tissues: pericardium, 54 (22.4 per cent), spleen, 174 (72.2 per cent), liver, 145 (60.2 per cent), kidneys, 73 (30.3 per cent), intestines, 59 (24.5 per cent), peritoneum, 56 (23.2 per cent), and mesenteric lymph nodes, 111 (46.1 per cent). No distinction is made between childhood and adult type tuberculosis in the above figures. The impression one obtains, however, is that these cases were largely childhood type tuberculosis. In our series of 37 childhood and 76 adult cases of tuberculosis in Negroes, extrapulmonary lesions were found more frequently in the progressive pulmonary type of childhood tuberculosis (table 4) than in the adult type. The differences in frequency were found significant, however, only in the occur-



rence of caseous mesenteric lymph nodes and tuberculous lesions in the spleen, and possibly in those involving the peritoneum

#### SUMMARY

1 Autopsy findings are reported for 113 Negroes dying of pulmonary tuberculosis in Jamaica, classified as 37 cases of progressive childhood type and 76 cases of adult type

2 The average age, duration of illness and length of urban residence were materially less in those cases designated as childhood type tuberculosis

3 Pleuritic involvement was present in a large proportion of cases and with about equal frequency in both groups

4 The disease originated in one of the upper lobes in 60 per cent of the childhood type group and in 98.7 per cent of the adult type group

5 Cavity formation occurred most frequently in one of the upper lobes in both adult and childhood types

6 In childhood type tuberculosis caseous pneumonia was the predominant pulmonary tissue reaction, while in the adult type the most frequent and characteristic tissue reaction was fibrous tissue formation

7 Extrapulmonary lesions secondary to the pulmonary disease occurred in both groups of cases, but more frequently in those cases designated as progressive childhood type tuberculosis

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## CASE REPORTS

### ANTHRACOSILICOSIS SIMULATING PULMONARY CARCINOMA<sup>1</sup>

With Report of a Case

HOWARD H. BRADSHAW AND RICHARD J. CHODOFF

Thoracic surgery has made such tremendous advances in recent years that exploratory thoracotomy is no longer considered a "last hope" procedure in the study and treatment of obscure thoracic lesions. Its place in the fight against pulmonary carcinoma is recognized. Certainly one should not hesitate to recommend exploration in those cases in which the diagnosis remains in doubt after conservative measures have failed. Examples in which even exploration of the thorax fails to make a correct diagnosis are fortunately rare. However, they occur. Overholt (1) reports a case in which the diagnosis of pulmonary neoplasm was made on the basis of X-ray shadows and symptoms of cough, haemoptysis and loss of weight. At operation it was felt that the lung was the site of a malignant lesion and pneumonectomy was carried out. Examination of the specimen proved the lesion to have been a circumscribed lung abscess. Overholt stresses the fact that even palpation of the lung at operation may leave the diagnosis in doubt. His opinion, with which we agree, is that lobectomy or pneumonectomy may prove to be the safest procedure in these cases.

Recently we had under our observation a patient presenting symptoms and radiological evidence that seemed typical of pulmonary carcinoma. There was also a long history of exposure to coal dusts. At operation the diagnosis of pulmonary carcinoma was made and a total pneumonectomy performed. The lesion proved to be anthracosilicosis. The case is reported here in detail.

#### *Case Report*

W. W., male, age 34, was admitted to Jefferson Hospital on December 3, 1936, complaining of cough, expectoration, loss of weight and shortness of breath for the past nine months. The past history was irrelevant except

<sup>1</sup> From the Surgical Service of Dr. George P. Muller, Jefferson Medical College Hospital, Philadelphia, Pennsylvania.

for the occupational history. At the age of thirteen he began working in the coal mines, continuing intermittently for four years. Following this he spent one year in a viscose mill. The subsequent six years he worked in a railroad roundhouse, in an atmosphere full of soft coal smoke. He then spent a year as a rock driller in an anthracite mine, leaving this job, he worked as a gas station attendant up to the time of illness. When first taken sick he was admitted to Williamsport, Pennsylvania Hospital. His sputum was repeatedly negative for tubercle bacilli. An X-ray film of the chest taken here was reported as follows: "Left diaphragm smooth, right pulled up by adhesions. Area of dense clouding about size of half dollar at right hilum fading out into normal lung. Below and somewhat external to this is another smaller area of feathery clouding. This resembles lung abscess but a positive diagnosis cannot be made by X-ray. A bronchogenic neoplasm or mass of tuberculous hilar nodes cannot be ruled out. Left lung is negative."

No diagnosis could be made and he was referred to Jefferson Hospital for further study. On December 3, 1936, bronchoscopy was performed by Dr. L. Clerf, who reported "some bleeding from the right lower lobe bronchus. There is distortion of the right middle lobe bronchus but nothing was noted to suggest neoplasm nor was there sufficient secretion observed to suggest abscess."

An X-ray film taken on December 4, 1936 was reported as follows: "The chest shows a density close to the right root area extending up toward the upper lobe. It is fairly well circumscribed but there is some radiation into the surrounding tissues. It is suggestive of a malignant lesion. There are increased pulmonary markings in the right lower lobe, otherwise the lungs have a normal appearance. Slight displacement of the trachea to the right" (Figure 1).

Sputum examinations were repeatedly negative for tubercle bacilli. On December 12, 1936 Doctor Clerf reported that from the bronchoscopic examination "there is undoubted obstruction to the right upper lobe bronchus. Tendency for the mucosa to bleed." Iodized oil was instilled bronchoscopically on December 14, 1936 and a bronchogram taken. The report was "Close to the orifice of the right upper lobe bronchus the oil has collected in several small pools and also has scattered in an irregular fashion in the lung

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FIG 1 X-ray film taken on December 4, 1936. A circumscribed area of density is seen at the right root area.

FIG 2 X-ray film taken on December 14, 1936, after bronchoscopic instillation of iodized oil. Pooling of the oil in the right root area shows evidence of destruction of lung tissue.

FIG 3 Lateral X-ray film of chest taken on December 23, 1936.

FIG 4 X-ray film taken on May 5, 1938, after two courses of roentgen therapy. Upward retraction of hilum is seen.

FIG 5 Lateral view taken on May 5, 1938.

Fig 1



Fig 2



Fig 3



Fig 4



Fig 5



tissue about it. Part of the bronchial tree is outlined, having a normal appearance. The manner of collection of the oil suggests possible abscess formation or destruction of the lung tissue by some pathological process" (Figure 2). A film of the chest, made on December 17, 1936, at the end of expiration, showed that "the right lower lobe empties well but there appears to be obstructive emphysema of the right upper lobe." On December 19, 1936 bronchoscopy was repeated. The observations were "Right upper lobe bronchus investigated. No definite evidence of growth. There is, however, something in the right upper lobe bronchus which bleeds readily when touched by forceps or aspirating tube. Material removed for examination." The material removed was reported by the laboratory as "inflammatory exudate." Further biopsy material was obtained on December 23, 1936 and reported as "blood clot and anthracotic tissue." Lateral X-ray films taken on December 23 demonstrated that the obstruction involved only the right upper lobe (Figure 3).

At no time during the patient's hospital stay did he have any elevation of temperature or of pulse rate. Haemoptysis did not occur. The diagnosis at this time remained in doubt. The history of exposure to dust suggested anthracosilicosis. Tuberculosis seemed unlikely in view of the nature of the X-ray films, the persistently negative sputum and the absence of fever or increased pulse rate. X-ray and bronchoscopy suggested that the most probable diagnosis was bronchogenic carcinoma, superimposed on anthracosilicosis. Exploratory thoracotomy was advised but the patient refused and returned to Williamsport on December 23, 1936.

At Williamsport, Pennsylvania Hospital on December 26, 1936 an X-ray film of the chest revealed an infiltrating mass in the hilum of the right lung which spread outward into the middle lobe and upper part of the lower lobe. This was thought to be a pulmonary carcinoma. Between January 4 and January 23, 1937 he was given a course of deep roentgen ray therapy. On February 10, 1937 a chest X-ray film presented no change in the appearance of the lesion. Subsequent films on February 22 and March 15, 1937 also showed no change. A second course of X-ray therapy was given between May 17 and June 11, 1937. On February 4, 1938 a chest X-ray film indicated that the lesion was more extensive than on previous studies.

On May 5, 1938 he was again admitted to Jefferson Hospital with a history of increasing dyspnoea, cough and expectoration. No haemoptysis had occurred. He had lost twenty-one pounds since his previous admission. An X-ray film taken the day of admission revealed "Considerable change in chest since last plate taken on December 21, 1936. Both hila are symmetrically and markedly elevated. In addition there is an increase in the fibrosis radiating upward and laterally from both hila. The left lower lobe field is emphysematous. The trachea is displaced to the right. A moderate amount

of lipiodol remains in the right upper lobe as a result of the previous pneumonography ' (Figures 4 and 5) Bronchoscopic examination on May 7, 1938 revealed ' The trachea is displaced to the right as is the right bronchus. The right upper lobe bronchial orifice is visualized without difficulty. At the level of the middle lobe bronchus the lumen is almost obliterated, the result of an extrabronchial lesion which is producing compression. There is no abnormal secretion present nor is there any inflammatory change in the mucosa. The observations suggest an extrabronchial lesion which is producing compression stenosis with deformity of the right bronchus, beginning at the level of the middle lobe '.

Diagnostic pneumothorax on the right side was attempted, but was unsuccessful presumably due to pleural adhesions. On May 13, 1938 an aspiration biopsy was done but no cellular elements were noted in the material obtained. As on the previous admission, temperature and pulse had remained normal.

Exploratory thoracotomy was again advised and the patient consented. On May 27, 1938 Dr. Howard Bradshaw performed the operation under endotracheal cyclopropane-ether-oxygen anaesthesia. A curved scapular incision was made and the fourth and fifth ribs resected. A small amount of clear fluid was encountered on opening the pleural cavity. A dense, broad adhesion was present between the apex of the right lung and the anterolateral chest wall. A few other adhesions were present. When the lung was freed a large mass was felt in its upper portion. It was stony hard and the pleural surface overlying it was covered by a grayish exudate. Grossly it appeared to be a typical pulmonary carcinoma. A few small nodes were felt about the hilum of the lung and along the trachea. Total pneumonectomy was performed. The major incision was closed tightly and drainage established by means of a tube through the seventh interspace. At the end of the operation a pneumothorax was discovered on the left side. The air was at once removed. The patient was placed in an oxygen tent and the intercostal tube attached to a suction pump with 3 cm. of water negative pressure. A transfusion of citrated blood was given and continuous intravenous glucose-saline started. Pneumothorax recurred on the left side and the patient died as the air was being withdrawn.

The pathological report of the excised lung by Dr. Baxter Crawford follows: "The pleural surface of the lung is thickened and ragged. The entire lung contains much black pigment and the upper three-quarters of the upper lobe is solid and nodular. On section this is composed of dense, consolidated black tissue. Small areas have broken down. The remainder of the lung contains a moderate amount of pigmentation and of fibrotic foci."

**Histology.** The lung parenchyma in the consolidated area is entirely replaced by dense fibrous tissue in which there is a large amount of black pig-

ment. The fibrous tissue is in the form of small nodules in areas which form hyalinized foci. In other areas the connective tissue is more cellular. Only a few atrophied bronchioles and air vesicles are observed in the tissue. At the apex there is marked thickening and fibrosis of the pleura. The small fibrotic nodules are suggestive of silicosis.

Diagnosis. Anthracosilicosis with extensive fibrosis and consolidation.

Autopsy (summary). Pulmonary anthracosis and fibrosis, localized, left apex. Chronic rheumatic endocarditis.

#### DISCUSSION

Whether the incidence of carcinoma of the lung is increased in pneumoconiosis is a debatable question, although the majority of observers to-day feel that carcinoma does not occur more often in the pneumoconiotic than in the normal lung. The often quoted example of the high incidence of pulmonary carcinoma in workers in the Schneeberg and St. Joachimstal mines is based on a misinterpretation of the facts.

According to Saupe (2) the aetiological factor in these cases is not the inorganic dust but the radioactive substances in the inhaled air. Vorwald and Karr (3) in a study of autopsies at Saranac found a percentage of pulmonary tumors of 0.074 in silicotics and of 0.014 in nonsilicotics. They quote the following figures from the miners' Phthisis Medical Bureau, South Africa:

	NUMBER OF AUTOPSIES	NUMBER OF CARCINOMA OF THE LUNG	PER CENT CARCINOMA
Miners with silicosis	1,438	10	0.70
Miners without silicosis	1,679	12	0.71
Males never underground	1,393	13	0.93

These figures indicate that pulmonary carcinoma is an unusual complication of silicosis.

In the occasional case in which carcinoma develops as a complication of pneumoconiosis the diagnosis is difficult. The symptoms and radiological findings of the primary disease may cloud or completely obscure those of the carcinoma. It may be impossible to prove the presence of carcinoma in an individual in which it is suspected, except at autopsy. Bronchoscopy is invaluable but is not infallible. X-ray studies may be of no help, as the increased hilar shadows of advanced silicosis may be mistaken for carcinoma. Gut (4) reported a case in which X-ray observations indicated the presence of a bronchogenic carcinoma. Shadows in the other lung led to the belief that metastatic lesions were

present. At autopsy it was noted that anthracotic induration at both hila had caused bronchostenosis and obstructive emphysema. Pancoast and Pendergrass (5) divide the X-ray findings in pneumoconiosis into three phases:

- 1: The phase of perivascular, peribronchial, lymph node enlargement. X-ray films show increased linear markings and enlarged hilar shadows.
- 2: The phase of early interstitial fibrosis. The lungs are homogeneously hazy. The hilar shadows are increased. Small nodules may be scattered throughout the lung fields.
- 3: The phase of nodular coalescence and fibrosis. This is the most characteristic picture of pneumoconiosis. Small, discrete nodules are present throughout both lungs. These may become conglomerate.

The phase of nodular coalescence as described by Pancoast and Pendergrass (5) corresponds to the end stages of lymphatic stasis, lymph node enlargement and massive fibrosis described by Gardner (6). The X-ray picture, although the increased hilar shadows may occasionally suggest carcinoma, usually shows enough of the associated features of pneumoconiosis to make the diagnosis reasonably certain. Gardner (7) states "in silicosis the first pathognomonic shadow is that of the fine nodule in the parenchyma of the lung field . . . one is not justified in diagnosing silicosis unless he sees the characteristic nodular shadows in the lung field." We feel that this statement is misleading, since many cases of silicosis do not show the typical nodular shadows Gardner describes. Massive hilar shadows may be present and may not be accompanied by nodular shadows in the rest of the lung. Fortunately, the bilateral, symmetrical nature of these shadows in pneumoconiosis usually serve to distinguish them from bronchogenic carcinoma, in which the shadow is usually unilateral. The difficulty sometimes encountered in differentiating pneumoconiosis from pulmonary neoplasm is recognized by Garland (8) who states that pulmonary tumors rarely simulate pneumoconiosis but that the converse is not infrequently seen. Large, coalescent fibrotic areas may resemble single or multiple metastatic tumors. Minet (9) and his associates have reported a roentgen study of miners whose lungs showed pseudotumoral shadows. Of these cases, only one in nine presented a single shadow. The statement of Hugenin that any pulmonary shadow, regardless of shape or form, may be due to carcinoma is questioned by these observers. They believe that the multiplicity of shadows in pneumoconiosis, as well as the long duration of the symp-



toms and the absence of haemoptysis are sufficient evidence to rule out carcinoma

In none of the reports on the roentgenological appearance of pneumoconiosis have we found a description of a single, enlarged hilar shadow, producing bronchostenosis and lobar emphysema and showing no evidence of nodular shadows in the rest of the lung fields. We must take exception, therefore, to Gardner's statement that one is not justified in diagnosing silicosis unless nodular shadows are seen.

#### SUMMARY AND CONCLUSIONS

A case is presented that illustrates the difficulty that sometimes arises in the diagnosis of intrathoracic lesions, and also emphasizes the fact that the accepted criteria for the recognition of pneumoconiosis need some revision. The symptoms of both diseases may be very similar. True, haemoptysis is seen more often in carcinoma but the presence or absence of a single symptom cannot be made the sole basis of a diagnosis. Neither pulmonary carcinoma nor pneumoconiosis respond to roentgen ray therapy. We believe, with Overholt, that, until the attitude of the medical profession toward exploratory thoracotomy approaches that which is current toward exploratory laparotomy, mistakes will happen. It will be only through the accumulation of experience in direct observation and palpation of pulmonary lesions that thoracic surgeons will be able to recognize pulmonary carcinoma as easily as the experienced abdominal surgeon is able to recognize, for example, carcinoma of the colon. Thoracic surgery has advanced to the point where the chest may be opened, if not with impunity, certainly with a reasonable assurance of safety.

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# AN UNUSUAL CASE OF TUBERCULOSIS OF THE SPINE

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The diagnostic criteria of tuberculosis of the spine are usually based on the late manifestations of the disease

Ornstein and Ulmar cite a number of instances where even in advanced cases of tuberculosis of the spine the roentgenographic findings were negative. The case to be reported illustrates the difficulty of making the diagnosis when the suggestive roentgenographic evidence is that of fracture rather than that of an inflammatory process

## *Case Report*

F K, a 25 year old colored male, was seen on January 27, 1937, giving a history of having sustained an injury to the spine on September 15, 1936. While carrying a crate of carrots weighing 150 pounds on his head, the patient slipped on the sidewalk and struck his back against the curbstone. The injury was sustained with the spine in extension rather than in flexion. He was able to get up and walk, but did not report to work on the following day because of pain. He consulted a private physician who treated him palliatively until November 11, 1936. Following this he went to a hospital where roentgenograms taken on November 19 showed no evidence of disease in the lumbar spine. He received symptomatic treatment with no improvement in his complaint of low back pain. Stereoscopic plates were then taken of this area (February, 1937) and the roentgenologist reported a break in the outline of the upper posterior border of the body of the third lumbar vertebra, suggesting an incomplete fracture at this site.

Our own examination indicated that there was no deformity of the spine, but that all motions of the back, especially lateral motions, were limited. There was spasm of the spinal muscles. Tenderness was present over both sacroiliac joints, over the sacrolumbar area and over the lumbar spinous processes. Our roentgenograms showed a free, roughly triangular fragment of bone, measuring 1.5 cm. in its long diameter, at the superior and posterior part of the third lumbar vertebra. It was displaced slightly upward. Although this is a rather atypical site of fracture of a lumbar vertebra, it was interpreted as an incomplete fracture (S S). It seemed that this part of the vertebra might have been injured by the fall in extension. He was placed in

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traction on a Bradford frame at the time of his first admission to the Hospital for Joint Diseases on March 6, 1937. On March 18, a plaster of paris jacket was applied. He was relieved of his pain for the most part by the support of the jacket and later a brace and by diathermy treatments. Dull pain was sometime present in rainy weather and on effort. There was always a slight residual muscle spasm and some limitation of motion, especially in lateral and forward flexion. The roentgenogram of August 21, 1937 indicated healing of the supposed fracture of the third lumbar vertebra. There was some narrowing of the adjacent intervertebral disc and osteoporosis of the body of the affected vertebra.

On September 8, 1937, one year after the original injury, the patient was seen at his home because of severe headache and vomiting for a period of eight days. This had been preceded by intermittent headache for two weeks, and a feeling of poor health. He was semistuporous but could be aroused to answer questions. He was then somewhat incoherent. The principal findings were a temperature of  $100.1^{\circ}\text{F}$ , nuchal rigidity, photophobia and bilateral Kernig and Brudzinski signs. He was immediately hospitalized with a diagnosis of meningitis. All deep reflexes were hyperactive. The Babinski sign was negative. A bilateral low grade papilloedema was noted. There were no tubercles seen in the fundus. Spinal tap on admission showed a clear fluid, with 173 lymphocytes per cc.

A roentgenogram of the chest on September 11, 1937 disclosed individual and conglomerate parenchymatous lobular infiltrations scattered throughout the right lung and the upper third of the left lung. This was considered to be due to a parenchymatous tuberculosis. A similar roentgenographic examination of the chest on September 20 showed that throughout both lungs there was a condition which resembled somewhat the early stage of miliary tuberculosis.

While in the hospital, the patient ran a temperature ranging from  $101^{\circ}$  to  $104.2^{\circ}\text{F}$ , the average temperature being about  $102.6^{\circ}\text{F}$ . The pulse rate was between 100 and 140, reaching 150 antemortem. The patient was markedly restless, requiring intravenous sedation by sodium amytal. He could take only fluids and vomited frequently. He was incoherent and poorly oriented. Spinal taps were done as a therapeutic measure under evipal anaesthesia. On September 19 the patient became semicomatose, developed localized muscle twitchings of the extremities and had brief spells of hiccoughing. He died on September 23, 1937.

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FIGS 1A and 1B Anteroposterior and lateral views of the lumbar spine show area of destruction which was mistaken for fracture

FIG 2 The sagittally cut autopsy specimen showing the areas of excision in the second and third lumbar vertebrae

FIG 3 Lateral roentgenogram of the autopsy specimen

FIG 1A



FIG 1B



FIG 2



FIG 3



On account of the demonstration of tubercle bacilli in the spinal fluid of September 14, it was thought that there might exist a relationship between the trauma sustained a year before and the present clinical picture. Roentgenograms of the lumbar spine were repeated on September 18, 1937 and interpreted by Dr. M. M. Pomeranz as follows: There is no kyphosis or scoliosis. There is a slight narrowing of the intervertebral disc between the bodies of the second and third lumbar vertebrae. In the right half of the body of the third lumbar vertebra, immediately below its superior surface, an abscess cavity approximately one inch in diameter is noted. The margins of this cavity are slightly sclerotic. The anterior part of the involved vertebra shows no specific alteration. There is no collapse of the vertebra nor any significant atrophy. There is a slight bulge in the psoas muscle on the right side. Conclusion: destructive process involving the second lumbar vertebra which has not the typical appearance of a tuberculous process.

Although roentgenographic evidence was not conclusive, clinically, one felt sufficiently certain of a causal relationship between the injury and the military tuberculosis so that a medical examiner's necropsy was insisted upon. The following pertinent findings on postmortem examination were reported. The lungs showed no calcified lymph nodes or primary complex. Military tubercles were present in the liver, the adrenal glands, the spleen and kidneys. An isolated, yellowish, subintimal nodule was seen in the thoracic portion of the aorta. The dura was adherent to the pia and arachnoid and brain substance by a plastic exudate in several areas over the convexity anteriorly. The pia and arachnoid were oedematous, and studded with numerous pin-head and several somewhat larger whitish and yellowish nodules. The largest of these attained the size of tuberculomata, one measuring 0.5 cm. in diameter. Similar findings, but to a lesser degree, were observed in the region of the base of the brain. Superficially, within the substance of the left occipital lobe, two larger yellowish foci were noted, which had softened cores and appeared to be tuberculomata. One of the foci was present inferiorly and the other superiorly.

The posterosuperior part of the third lumbar vertebra was destroyed and replaced by yellowish-white, caseated material. Moderate osteosclerosis was present about this caseated area. The adjacent second lumbar vertebra showed a very small area of destruction at its posteroinferior part. The abscesses within the two bodies communicated by a narrow zone between the dura and the posterior surfaces of the bodies. The vertebral bodies were not compressed. The intervertebral disc was slightly narrowed. There were bilateral psoas abscesses. No evidence of fracture was found, old or new. A roentgenogram of the sectioned body showed no fracture line.

Microscopical examination confirmed the gross findings in all details. Of particular interest was the finding of two tubercles in a myocardial section. The intimal aortic nodule was apparently a tuberculoma. A tubercle was found in the pancreas.

This case presents two points of interest, diagnostic and medico-legal. Trauma is a frequent cause of back pain. Roentgenography is a valuable diagnostic adjunct in diseases of the spine. In this case, the interpretive ability of clinicians and roentgenologists failed and the patient was treated for fracture of the spine for one year. Where diagnosis by roentgenogram is not definite and conclusive, the possibility of an inflammatory lesion should be considered. This should have been suspected earlier in this case because of the persistence of muscle spasm and limitation of motion, in the presence of an atypical roentgenographic picture. The site of involvement was not typical for fracture nor for tuberculosis.

Since this was a compensation case, the finding of tuberculosis added a complication to the legal aspect (which, ultimately, was decided in the patient's favor).

#### CONCLUSION

A case is presented to demonstrate the difficulties in making a diagnosis of spinal tuberculosis, when X-ray studies are inconclusive. The diagnosis of the initial lesion was not made until the occurrence of milary tuberculosis and tuberculous meningitis.

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# INDEX OF SUBJECTS AND AUTHORS

- Abscess, psoas, tuberculous, Paravertebral aspiration of, 338
- Accidental pneumoperitoneum, 537
- Active pulmonary tuberculosis, patients with, Routine bronchoscopy in, 617
- ADELMAN, MILTON H Variations in leucocytes, 70
- Adult, Haematogenous tuberculosis in the, 557
- , primary tuberculous infection in the, Pathology of, 236
- relief population of a small community, X-ray study of the, 666
- Adults, Primary infection in, 232
- , young, Pulmonary tuberculosis in, 9
- AMBERSON, J BURNS, JR, AND SOFER, WILLARD B Pulmonary tuberculosis in young adults, 9
- Anatomy, Roentgenological, of the chest, 516
- ANDERSON, R S See MCINDOE, R B, *et al*, 617
- Anergy, Tuberculin, and the variability of tuberculins, (editorial), 551
- , —, in cases with pulmonary calcifications, 64
- Aneurysm, pulmonary arterial, in tuberculous cavities, Pathology and pathogenesis of, 99
- Anthracoilicosis simulating pulmonary carcinoma, 817
- Artificial pneumothorax, Chlorine for the induction of, 172
- Aspiration, Paravertebral, of tuberculous psoas abscess, 338
- Asynchrony of the movement of the lower ribs following paralysis of the hemidiaphragm, 169
- AUERBACH, OSCAR Pathology and pathogenesis of pulmonary arterial aneurysm in tuberculous cavities, 99
- Bacilli, tubercle, Demonstration of, by culture and by guinea pig inoculation, 397
- Bacilli, tubercle, Effects of ultraviolet radiation on, 782
- , —, in sputum, 89
- , —, Virulence of, 116
- BCG vaccination, Multiple puncture method of, 128
- BENNETT, EDWIN S, AND BOGEN, EMIL Tubercle bacilli in sputum, 89
- BERG, MELVIN See CUMMINGS, DONALD E, *et al*, 439
- Bilateral tuberculous pleurisy with effusion, 745
- BILLER, S B, AND PERLA, DAVID Extrapulmonary complications of pulmonary tuberculosis, 215
- Biological abstracts, (editorial), 135
- Blastomycosis, 275, 488
- BLOOR, WALTER R, AND ROOT, HOWARD F Diabetes and pulmonary tuberculosis, 714
- BOGEN, EMIL Life expectancy in tuberculosis, 587
- , —, AND BENNETT, EDWIN S Tubercle bacilli in sputum, 89
- BOOKS
- BANNEN, J E The radiology of pulmonary tuberculosis, 136
- POLLITZER, GUIDO Digrafia A new radiographic method for the examination of mobile organs, 137
- COULAUD, E Le pneumothorax bilatéral simultané, 138
- FRANCILLON, JACQUES Le pneumothorax extra-pleural chirurgical, 139
- MOROZOVSKI, N S, AND ALEXANDROVSKI, B P Parahilar tuberculosis in adults (Russian), 140
- HENDERSON, YANDELL Adventures in respiration, modes of asphyxiation and methods of resuscitation, 141
- BURKE, RICHARD M A historical chronology of tuberculosis, 141
- JACQUEROD, M Le traitement de la tuberculose pulmonaire par la tuberculine, 142



- STEHMAN, JACQUES Séniologie radio-graphique pulmonaire, 113
- KIER, NOEL L'Allergie conférée par les bacilles tuberculeux morts enrobés dans les paraffines, 113
- JACOBSON, EDWARD You can sleep well, 113
- ACERVEDO, ROBERTO CECILIA La duración de la colapsoterapia gaseosa y el problema de su interrupción, 113
- Birth, stillbirth, and infant mortality statistics, 1935, U. S. Department of Commerce, Bureau of the Census, 143
- Brompton Hospital Reports, 141
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- HORRIS, JOSEPH Immune blood therapy of tuberculosis, 141
- MARRAS, ERIC M. The technique of contraception, 141
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- NORMAN, GEORGE W., AND LINDSAY, H. R. M. Diseases of the chest and the principles of physical diagnosis, 144
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- UPHILL, KARL Die chirurgie des Kropfes, 144
- WILLS, C. W., AND SMITH, H. H. The epidemiology of tuberculosis in Kingston, Jamaica, B. W. I., 144
- BOSWORTH, HOWARD W., AND SMITH, C. RICHARD Collapse therapy in pulmonary tuberculosis, 33
- BOYNTON, RUTH E. The incidence of tuberculous infection in student nurses, 671
- BRADSHAW, HOWARD H., AND CHODOFF, RICHARD J. Anthraco-silicosis simulating pulmonary carcinoma, 817
- Bronchial catheterization, 329
- Bronchoscopy, Diagnostic, in occult tuberculosis, 629
- , Routine, in patients with active pulmonary tuberculosis, 617
- BRANT, JAMES CLIFF Oral tuberculosis, 735
- BURMAN, MICHAEL S. See FOX, THEODORE I., *et al.*, 825
- Calcifications, pulmonary, Tuberculin anergy in cases with, 64
- Carcinoma, pulmonary, Anthraco-silicosis simulating, 817
- Case fatality rates in tuberculosis, 597
- Case finding, 256
- Catheterization, Bronchial, 329
- Cavities, tuberculous, pulmonary arterial aneurysm in, Pathology and pathogenesis of, 99
- Chest, Roentgenological anatomy of the, 516
- , Sectional roentgenography of the, 204
- CHIU, PHILIP T. Y. See MARFAS, J. ARTHUR, *et al.*, 232
- Chlorine for the induction of artificial pneumothorax, 172
- CHODOFF, RICHARD J., AND BRADSHAW, HOWARD H. Anthraco-silicosis simulating pulmonary carcinoma, 817
- Climatic and socio-economic factors in mortality from pulmonary tuberculosis, 305
- Coccidioides infection, 266
- Collapse therapy in pulmonary tuberculosis, 33
- , Protamine insulin and, in diabetes complicated by pulmonary tuberculosis, 181
- Community, entire, Tuberculosis survey of an, 778
- , small, X-ray study of the adult relief population of, 666
- Complications, Extrapulmonary, of pulmonary tuberculosis, 215
- Control, Tuberculosis, in industry, 456
- CRIMM, PAUL D., AND SHORT, DARWIN M. Tuberculin anergy in cases with pulmonary calcifications, 64
- Cultural methods in the diagnosis of tuberculosis, 540
- Culture, Demonstration of tubercle bacilli by, and by guinea pig inoculation, 397
- CUMMINGS, DONALD E., DOWNS, ROBERT N., AND BRECK, MELVIN Tuberculous lesions in male industrial workers, 439

- DASGUPTA, H. N. See RAY, K. S., *et al.*, 172
- DAUER, C. C. Tuberculosis mortality in industrial populations of Massachusetts and Michigan, 605
- DAVIES, ROBERTS, AND SCHERER, C. A. Tuberculosis survey of an entire community, 778
- DE CICIO, THOMAS, AND ELWOOD, BENJAMIN J. Erythrocyte sedimentation, 748
- , —, —, —, —, — Serial leucocyte counts, 641
- Demonstration of tubercle bacilli by culture and by guinea pig inoculation, 397
- Densitization, tuberculin, Treatment of tuberculosis by, 318
- Detection of tuberculosis in group surveys, 766
- Diabetes and pulmonary tuberculosis, 714
- complicated by pulmonary tuberculosis, Protamine insulin and collapse therapy in, 181
- Diagnosis of tuberculosis, Cultural methods in the, 540
- Diagnostic bronchoscopy in occult tuberculosis, 629
- DOLLEY, FRANK S., AND JONES, JOHN C. Surgical treatment of tumors of lung and mediastinum, 479
- , —, —, —, —, —, AND PAXTON, JOHN R. Late results of thoracoplasty, 145
- DOWNS, ROBERT N. See CUMMINGS, DONALD E., *et al.*, 439
- DROLET, GODIAS J. Case fatality rates in tuberculosis, 597
- Dusts, Industrial, and the mortality from pulmonary disease, 419
- EATON, J. LLOYD See TRIMBLE, HAROLD GUYON, *et al.*, 528
- EDITORIAL. Biological abstracts, 135
- Tuberculin anergy and the variability of tuberculin, 551
- Effect of tuberculosis on the serological reactions for syphilis, 1
- Effects of ultraviolet radiation on tubercle bacilli, 782
- Effusion, Bilateral tuberculous pleurisy with, 745
- , Pleural, 57
- ELWOOD, BENJAMIN J. Protamine insulin and collapse therapy in diabetes complicated by pulmonary tuberculosis, 181
- , —, —, —, AND DE CICIO, THOMAS Erythrocyte sedimentation, 748
- , —, —, —, —, — Serial leucocyte counts, 641
- EMERSON, KENDALL, AND PARRAN, THOMAS The effect of tuberculosis on the serological reactions for syphilis, 1
- Epidemiological aspects of the negative tuberculin reaction, 754
- Epithelioid cells of inflammatory exudates, polymorphonuclear leucocytes, monocytes and, Proteinase and peptidase activity of, 228
- Erythrocyte sedimentation, 748
- Extrapulmonary complications of pulmonary tuberculosis, 215
- Exudates, inflammatory, Proteinase and peptidase activity of polymorphonuclear leucocytes, monocytes and epithelioid cells of, 228
- Factors of healing, latency and progression in pulmonary tuberculosis, 348
- FARNES, O. J., AND MILLS, CHARLES W. Coccidioides infection, 266
- Fatality rates in tuberculosis, Case, 597
- FINKELSTEIN, MAX, AND GUGGENHEIM, ALBERT The demonstration of tubercle bacilli by culture and by guinea pig inoculation, 397
- FLANCE, I. J., AND WHEELER, P. A. Post-mortem incidence of tuberculous tracheo-bronchitis, 633
- Florida, Tuberculosis survey in, 408
- FOX, THEODORE T., BURMAN, MICHAEL S., AND SINBERG, SAMUEL An unusual case of tuberculosis of the spine, 825
- Friction rub, Precordial, in spontaneous pneumothorax, 176
- GAETÁN, L. R. Accidental pneumoperitoneum, 537
- Group surveys, Detection of tuberculosis in, 766

- GUGGENHEIM, ALBERT, AND FISCHLSTEIN, MAX The demonstration of tubercle bacilli by culture and by guinea pig inoculation, 397
- Guinea pig inoculation, Demonstration of tubercle bacilli by culture and by, 397
- pigs, tuberculosis of, Vitamin C and immunity in, 794
- Haematogenous tuberculosis in the adult, 557
- HAWKINS, J LAWRENCE H, JR Tuberculous tracheobronchitis, 46
- HEAD, JEROME R Asynchrony of the movement of the lower ribs following paralysis of the hemidiaphragm, 169
- Healing, latency and progression in pulmonary tuberculosis, Factors of, 348
- HEIST, FRED H, AND SCHWARTZ, SPENCER Olive oil in pneumothorax, 651
- , —, — STEFANEN, WILLIAM, JR Vitamin C and immunity in tuberculosis of guinea pigs, 794
- Hemidiaphragm, paralysis of the, Asynchrony of the movement of the lower ribs following, 169
- HERRINGTON, L P, AND MORIYAMA, I M Climatic and socio economic factors in mortality from pulmonary tuberculosis, 305
- HORTON, RALPH, LINCOLN, N STANLEY, AND PRYER, MAX Noncascating tuberculosis, 186
- Immunity, Vitamin C and, in tuberculosis of guinea pigs, 794
- Incidence of tuberculous infection in student nurses, 671
- , Postmortem, of tuberculous tracheobronchitis, 633
- Industrial dusts and the mortality from pulmonary disease, 419
- populations of Massachusetts and Michigan, Tuberculosis mortality in, 603
- workers, male, Tuberculous lesions in, 439
- Industry, Tuberculosis control in, 456
- Infection, Primary, in adults, 232
- , — tuberculous, in the adult, Pathology of, 236
- Infection, tuberculous, in student nurses, Incidence of, 671
- Insulin, Protamine, and collapse therapy in diabetes complicated by pulmonary tuberculosis, 181
- Intrapleural pneumonolysis by the closed method, 162
- Jamaican Negroes, pulmonary tuberculosis among, Pathological changes in, 796
- JOCZ, T R, AND WILLIS, HENRY STUART Treatment of tuberculosis by tuberculin desensitization, 318
- JONES, JOHN C, AND DOLLEY, FRANK S Surgical treatment of tumors of lung and mediastinum, 479
- , — — See DOLLEY, FRANK S, *et al*, 145
- KAMPMEIER, R H, AND KELLER, A E Tuberculin survey, 657
- KELLER, A E, AND KAMPMEIER, R H Tuberculin survey, 657
- KELLY, RUBY G, AND WILLIS, HENRY STUART Results of intensive study of sputum in pulmonary tuberculosis, 81
- KENT, EDWARD M, AND WARRING, FREDERICK C, JR Paravertebral aspiration of tuberculous psoas abscess, 338
- KRIES, PHILLIP T The detection of tuberculosis in group surveys, 766
- LANZA, A J, AND VANE, R J Industrial dusts and the mortality from pulmonary disease, 419
- Late results of thoracoplasty, 145
- Latency, healing, and progression in pulmonary tuberculosis, Factors of, 348
- LAVIN, GEORGE I, AND SMITHBURN, KENNETH C The effects of ultraviolet radiation on tubercle bacilli, 782
- Lesions, Tuberculous, in male industrial workers, 439
- LESLIE, G L See MCINDOE, R B, *et al*, 617
- Leucocyte counts, Serial, 641
- Leucocytes, polymorphonuclear, monocytes and epithelioid cells of inflammatory exudates, Proteinase and peptidase activity of, 228
- , Variations in, 70

- Life expectancy in tuberculosis, 587
- LINCOLN, N STANLEY See HORTON, RALPH, *et al*, 186
- LINDBERG, D O N An X-ray study of the adult relief population of a small community, 666
- LOGIE, ARTHUR J Tuberculosis survey in Florida, 408
- LONG, ESMOND R Tuberculin anergy and the variability of tuberculin, (editorial), 551
- LOURIA, MILTON R Precordial friction rub in spontaneous pneumothorax, 176
- Lung and mediastinum, tumors of, Surgical treatment of, 479
- MARTIN, DONALD S, AND SMITH, DAVID T Blastomycosis, 275, 488
- Massachusetts and Michigan, industrial populations of, Tuberculosis mortality in, 603
- MATSON, RALPH C Intrapleural pneumonolysis by the closed method, 162
- MCINDOE, R B, STEELE, JOHN D, SAMSON, PAUL C, ANDERSON, R S, AND LESLIE, G L Routine bronchoscopy in patients with active pulmonary tuberculosis, 617
- Mediastinum, tumors of lung and, Surgical treatment of, 479
- Michigan, industrial populations of Massachusetts and, Tuberculosis mortality in, 603
- MILLS, CHARLES W, AND FARNES, O J Coccidioides infection, 266
- Monkeys, rhesus, Spontaneously acquired tuberculosis in, 675
- Monocytes, polymorphonuclear leucocytes, and epitheloid cells of inflammatory exudates, Proteinase and peptidase activity of, 228
- MOORE, GERTRUDE See TRIMBLE, HAROLD GUYON, *et al*, 528
- MORIYAMA, I M, AND HERRINGTON, L P Climatic and socio-economic factors in mortality from pulmonary tuberculosis, 305
- Mortality from pulmonary disease, Industrial dusts and the, 419
- tuberculosis, Climatic and socio economic factors in, 305
- Mortality, Tuberculosis, in industrial populations of Massachusetts and Michigan, 603
- Multiple puncture method of BCG vaccination, 128
- MYERS, J ARTHUR, CH'IU, PHILIP T Y, AND STREUKENS, THEODORE L, JR Primary infection in adults, 232
- Negroes, Jamaican, pulmonary tuberculosis among, Pathological changes in, 796
- Noncaseating tuberculosis, 186
- Nurses, student, tuberculous infection in, Incidence of, 671
- Occult tuberculosis, Diagnostic bronchoscopy in, 629
- Olive oil in pneumothorax, 651
- Oral tuberculosis, 738
- Paralysis of the hemidiaphragm, Asynchrony of the movement of the lower ribs following, 169
- Paravertebral aspiration of tuberculous psoas abscess, 338
- PARETZKY, M The epidemiological aspects of the negative tuberculin reaction, 754
- PARRAN, THOMAS, AND EMERSON, KENDALL The effect of tuberculosis on the serological reactions for syphilis, 1
- Pathogenesis, Pathology and, of pulmonary arterial aneurysm in tuberculous cavities, 99
- Pathological changes in pulmonary tuberculosis among Jamaican Negroes, 796
- Pathology and pathogenesis of pulmonary arterial aneurysm in tuberculous cavities, 99
- of primary tuberculous infection in the adult, 236
- Patients with active pulmonary tuberculosis, Routine bronchoscopy in, 617
- PAXTON, JOHN R See DOLLEY, FRANK S, *et al*, 145
- PEIRCE, CARLETON B, AND STOCKING, BRUCE W The roentgenological anatomy of the chest, 516
- Peptidase, Proteinase and, activity of polymorphonuclear leucocytes, monocytes and epitheloid cells of inflammatory exudates, 228

- PERLA, DAVID, AND BIEFF, S. B. Extra pulmonary complications of pulmonary tuberculosis, 215
- PINOFF, MAX. Biological abstracts, (editorial), 135
- , ——— See HORTON, RALPH, *et al*, 186
- Pleural effusion, 57
- Pleurisy, tuberculous, Bilateral, with effusion, 745
- PLUNKETT, ROBERT E. Case finding, 256
- Pneumonolysis, Intripleural, by the closed method, 162
- Pneumoperitoneum, Accidental, 537
- in the treatment of pulmonary tuberculosis, 528
- Pneumothorax, artificial, Chlorine for the induction of, 172
- , Olive oil in, 651
- , spontaneous, Precordial friction rub in, 176
- Polymorphonuclear leucocytes, monocytes and epithelioid cells of inflammatory exudates, Proteinase and peptidase activity of, 228
- Postmortem incidence of tuberculous tracheobronchitis, 633
- Precordial friction rub in spontaneous pneumothorax, 176
- Primary infection in adults, 332
- tuberculous infection in the adult, Pathology of, 236
- Progression, healing, latency and, in pulmonary tuberculosis, Factors of, 348
- Protamine insulin and collapse therapy in diabetes complicated by pulmonary tuberculosis, 181
- Proteinase and peptidase activity of polymorphonuclear leucocytes, monocytes and epithelioid cells of inflammatory exudates, 228
- Psoas abscess, tuberculous, Paravertebral aspiration of, 338
- Pulmonary arterial aneurysm in tuberculous cavities, Pathology and pathogenesis of, 99
- carcinoma, Anthracosilicosis simulating, 817
- disease, mortality from, Industrial dusts and the, 419
- Pulmonary tuberculosis, active, patients with, Routine bronchoscopy in, 617
- among Jamaican Negroes, Pathological changes in, 796
- , Collapse therapy in, 33
- , Diabetes and, 711
- , ——— complicated by, Protamine insulin and collapse therapy in, 181
- , Extrapulmonary complications of, 215
- , Factors of healing, latency and progression in, 348
- in the second decade of life, 683, 703
- ——— young adults, 9
- , mortality from, Climatic and socio economic factors in, 305
- , Results of intensive study of sputum in, 81
- , treatment of, Pneumoperitoneum in the, 528
- Radiation, ultraviolet, Effects of, on tubercle bacilli, 782
- RAY, K. S., SEN, N. N., AND DASGUPTA, H. N. Chlorine for the induction of artificial pneumothorax, 172
- Reaction, tuberculin, negative, Epidemiological aspects of the, 754
- Reactions, serological, for syphilis, Effect of tuberculosis on the, 1
- Relief population, adult, of a small community, X ray study of the, 666
- Resistance to tuberculosis, 371, 383
- Results, Late, of thoracoplasty, 145
- of intensive study of sputum in pulmonary tuberculosis, 81
- Roentgenography, Sectional, of the chest, 204
- Roentgenological anatomy of the chest, 516
- ROOT, HOWARD F., AND BLOOR, WALTER R. Diabetes and pulmonary tuberculosis, 714
- ROSENTHAL, SOL ROY. The multiple puncture method of BCG vaccination, 128
- Routine bronchoscopy in patients with active pulmonary tuberculosis, 617
- RUBIN, ELI H. Hematogenous tuberculosis in the adult, 557
- RUDMAN, I. ELLIS. Bronchial catheterization, 329

- SAMSON, PAUL C See McINDOE, R B, *et al*, 617
- SAWYER, W A Tuberculosis control in industry, 156
- SCHERER, C A, AND DAVIES, ROBERTS Tuberculosis survey of an entire community, 778
- SCHWARTZ, SPENCER, AND HEISE, FRED H Olive oil in pneumothorax, 651
- Second decade of life, Pulmonary tuberculosis in the, 683, 703
- Sectional roentgenography of the chest, 204
- Sedimentation, Erythrocyte, 748
- SEN, N N See RAY, K S, *et al*, 172
- Serul leucocyte counts, 641
- Serological reactions for syphilis, Effect of tuberculosis on the, 1
- SHIPMAN, SIDNEY J Diagnostic bronchoscopy in occult tuberculosis, 629
- SHORT, DARWIN M, AND CRIMM, PAUL D Tuberculin anergy in cases with pulmonary calcifications, 64
- SINBERG, SAMUEL See FOX, THEODORE T, *et al*, 825
- SMITH, C RICHARD, AND BOSWORTH, HOWARD W Collapse therapy in pulmonary tuberculosis, 33
- SMITH, DAVID T, AND MARTIN, DONALD S Blastomycosis, 275, 488
- SMITHBURN, KENNETH C Resistance to tuberculosis, 371, 383
- , — Spontaneously acquired tuberculosis in rhesus monkeys, 675
- , — Virulence of tubercle bacilli, 116
- , —, AND LAVIN, GEORGE I The effects of ultraviolet radiation on tubercle bacilli, 782
- Socio economic factors, Climatic and, in mortality from pulmonary tuberculosis, 305
- SOPER, WILLARD B, AND AMBERSON, J BURNS, JR Pulmonary tuberculosis in young adults, 9
- Spine, tuberculosis of the, Unusual case of, 825
- Spontaneous pneumothorax, Precordial friction rub in, 176
- Spontaneously acquired tuberculosis in rhesus monkeys, 675
- Sputum, intensive study of, Results of, in pulmonary tuberculosis, 81
- , Tubercle bacilli in, 89
- STEELE, JOHN D See McINDOE, R B, *et al*, 617
- STEENKEN, WILLIAM, JR, AND HEISE, FRED H Vitamin C and immunity in tuberculosis of guinea pigs, 794
- STOCKING, BRUCE W, AND PEIRCE, CARLETON B The roentgenological anatomy of the chest, 516
- STREUKENS, THEODORE L, JR See MYERS, J ARTHUR, *et al*, 232
- Study, X-ray, of the adult relief population of a small community, 666
- Surgical treatment of tumors of lung and mediastinum, 479
- Survey, Tuberculin, 657
- , Tuberculosis, in Florida, 408
- , —, of an entire community, 778
- Surveys, group, Detection of tuberculosis in, 766
- SWEANY, HENRY C Factors of healing, latency and progression in pulmonary tuberculosis, 348
- , — The pathology of primary tuberculous infection in the adult, 236
- Syphilis, serological reactions for, Effect of tuberculosis on the, 1
- Therapy, Collapse, in pulmonary tuberculosis, 33
- , —, Protamine insulin and, in diabetes complicated by pulmonary tuberculosis, 181
- Thoracoplasty, Late results of, 145
- Tracheitis, Tuberculous, 637
- Tracheobronchitis, Tuberculous, 46
- , —, Postmortem incidence of, 633
- Treatment of pulmonary tuberculosis, Pneumoperitoneum in the, 528
- , — tuberculosis by tuberculin desensitization, 318
- , Surgical, of tumors of lung and mediastinum, 479
- TRIMBLE, HAROLD GUYON, EATON, J LLOYD, AND MOORE, GERTRUDE Pneumoperitoneum in the treatment of pulmonary tuberculosis, 528
- TRUDEAU, FRANCIS B Pleural effusion, 57

- Tubercle bacilli, Demonstration of, by culture and by guinea pig inoculation, 397
- — —, Effects of ultraviolet radiation on, 782
- — — in sputum, 89
- — —, Virulence of, 116
- Tuberculin allergy and the variability of tuberculins, (editorial), 551
- — — in cases with pulmonary calcifications, 64
- — — desensitization, Treatment of tuberculosis by, 318
- — — reaction, negative, Epidemiological aspects of the, 751
- — — survey, 657
- Tuberculins, variability of, Tuberculin allergy and the, (editorial), 551
- Tuberculosis, Case fatality rates in, 597
- — — control in industry, 456
- — —, Detection of, in group surveys, 766
- — —, diagnosis of, Cultural methods in the, 540
- — —, Effect of, on the serological reactions for syphilis, 1
- — —, Haematogenous, in the adult, 557
- — —, Life expectancy in, 587
- — — mortality in industrial populations of Massachusetts and Michigan, 603
- — —, Noncascating, 186
- — —, occult, Diagnostic bronchoscopy in, 629
- — — of guinea pigs, Vitamin C and immunity in, 794
- — — the spine, Unusual case of, 825
- — —, Oral, 738
- — —, pulmonary, active, patients with, Routine bronchoscopy in, 617
- — —, among Jamaican Negroes, Pathological changes in, 796
- — —, — — —, Collapse therapy in, 33
- — —, — — —, Diabetes and, 714
- — —, — — —, — — — complicated by, Protamine insulin and collapse therapy in, 181
- — —, — — —, Extrapulmonary complications of, 215
- — —, — — —, Factors of healing, latency and progression in, 348
- Tuberculosis, pulmonary, in the second decade of life, 683, 703
- — —, — — —, young adults, 9
- — —, — — —, mortality from, Climatic and socio economic factors in, 305
- — —, — — —, Results of intensive study of sputum in, 81
- — —, — — —, treatment of, Pneumopentoneum in the, 528
- — —, Resistance to, 371, 383
- — —, Spontaneously acquired, in rhesus monkeys, 675
- — — survey in Florida, 408
- — — of an entire community, 778
- — —, Treatment of, by tuberculin desensitization, 318
- Tuberculous infection in student nurses, Incidence of, 671
- — — lesions in male industrial workers, 439
- — — pleurisy, Bilateral, with effusion, 745
- — — psoas abscess, Paravertebral aspiration of, 338
- — — tracheitis, 637
- — — tracheobronchitis, 46
- — —, Postmortem incidence of, 633
- Tumors of lung and mediastinum, Surgical treatment of, 479
- Ultraviolet radiation, Effects of, on tubercle bacilli, 782
- Unusual case of tuberculosis of the spine, 825
- Vaccination, BCG, Multiple puncture method of, 128
- VANF, R. J., AND LANZA, A. J. Industrial dusts and the mortality from pulmonary disease, 419
- Variations in leucocytes, 70
- Virulence of tubercle bacilli, 116
- Vitamin C and immunity in tuberculosis of guinea pigs, 794
- WARRING, FREDERICK C., JR., AND KENT, EDWARD M. Paravertebral aspiration of tuberculous psoas abscess, 338
- WEISS, CHARLES. Proteinase and peptidase activity of polymorphonuclear leucocytes, monocytes and epithelioid cells of inflammatory exudates, 228

- WELLS, C W Pathological changes in pulmonary tuberculosis among Jamaican Negroes, 796
- WERNER, WALTER I Tuberculous tracheitis, 637
- WHITTLE, P A, AND FLANCH, I J Post-mortem incidence of tuberculous tracheobronchitis, 633
- WHITTENRAD, HUGH G Cultural methods in the diagnosis of tuberculosis, 540
- WILLIS, HELEN STUART, AND JOZ, T R Treatment of tuberculosis by tuberculin desensitization, 318
- , —, —, — KELL, RUDY G Results of intensive study of sputum in pulmonary tuberculosis, 81
- WILSON, GEORGE C Bilateral tuberculous pleurisy with effusion, 745
- Workers, industrial, male, Tuberculous lesions in, 439
- X-ray study of the adult relief population of a small community, 666
- ZACKS, DAVID Pulmonary tuberculosis in the second decade of life, 683, 703
- ZINTHEO, CLARENCE J, JR Sectional roentgenography of the chest, 204





# INDEX OF ABSTRACTS OF TUBERCULOSIS

- Abdominal lymph nodes, Tuberculous disease of, 68
- Abcess, Lung, 9
- Adenitis, cervical, Tuberculous, 69
- Adenoids, tonsils and, tuberculosis of, Prognosis in, 68
- Adults, young, children and, in Cattaraugus County, Tuberculosis among, 51
- , —, in England, Prevention of tuberculosis among, 36
- Agassiz, C D S Pneumothorax in children, 53
- Age groups, different, Course and mortality of tuberculosis in, 40
- Aged, Tuberculin allergy in the, 47
- Allergy, Tuberculin, in the aged, 47
- Alveolar walls of cat, 77
- Amberson, J B, Jr Early pulmonary tuberculosis, 55
- Anderson, R S, and Leslie, G L Collapse measures, 3
- , —, —, —, —, — Collapse therapy results, 4
- Anthraco-silicosis, Carcinoma in, 19
- Apgar, Virginia See Humphreys, G H, *et al*, 84
- Aschoff bodies in tuberculous individuals, 34
- Aspects of the tuberculosis problem, 47
- Atelectasis, 27
- in children, 52
- Atypical spontaneous pneumothorax, 13
- Azygos lobe, 76
- Bacanu, C Azygos lobe, 76
- Baker-Bates, E T, and McGibbon, J E G Bronchoscopic investigation of haemoptysis of uncertain cause, 26
- Baldwin, Janet, and Thelander, H E Variability of findings in tuberculous meningitis, 72
- Baylor, J W, and Bordley, J, III Prognosis in tuberculosis of tonsils and adenoids, 68
- Belgium, rural, Incidence of tuberculous infection in school children in, 40
- Belgorod, S H Progressive primary complex, 76
- Benign tumors of bronchi, 17
- Binet, L, and Burstein, M Nitrogen metabolism in lung, 86
- Bliss, T L Bronchorrhoea, 8
- Block, M, and Rosenblüth, M B Pneumococcus pneumonia, 12
- Bobrowitz, I D, and Leon, J L Readmissions to a tuberculosis hospital, 63
- Boeck's sarcoid, 80
- Bogen, E, and Skillen, Jane Pregnancy and tuberculosis, 63
- Bone graft, Short, for spinal fusion, 76
- marrow changes in tuberculosis, 77
- tuberculosis, 73
- Bones, Multiple cystic tuberculosis of, in children, 55
- Bordley, J, III, and Baylor, J W Prognosis in tuberculosis of tonsils and adenoids, 68
- Böss, C Mediastinal cysts, 33
- Bovine infection, 62
- tuberculosis in humans in Great Britain, 46
- Boynton, Ruth E See Myers, J A, *et al*, 45
- Brain, Calcified tuberculoma of, 71
- Bronchi, Benign tumors of, 17
- , large, Stenosis of, in pulmonary tuberculosis, 62
- Bronchial carcinoma, 18
- Bronchiectases, Cystic, 8
- Bronchitis, Tuberculous, 63
- Bronchogenic distribution of fluid and particulate matter, 86
- Bronchomoniliasis, 6
- Bronchorrhoea, 8
- Bronchoscopic investigation of haemoptysis of uncertain cause, 26

- Bronchoscopy in tracheobronchial tuberculosis, 64
- Budelmann, G Vital capacity, 81
- Bulla, ruptured, of lung, Fatal spontaneous pneumothorax due to, 13
- Bullowa, J G M, and Greenbaum, Evelyn Pneumococcus type-VII pneumonia, 12
- Bumbalo, T S, and Jetter, W W Vitamin C in tuberculosis, 55
- , ———, ———, ———, ———, ———  
Vitamin C in tuberculosis in children, 54
- Burgin, L B, and Higgins, H L Phlyctenulosis, 71
- Burke, R M Vanishing lungs, 24
- Burstein, M, and Binet L Nitrogen metabolism in lung, 86
- Calcified tuberculoma of brain, 71
- Calves, sensitized, Leucocytic response in, 88
- Campbell, J A Oxygen administration with box mask and face tent, 35
- Canadian hospital workers, Tuberculosis in, 45
- Cannetti, G, and Saenz, A Spontaneous tuberculosis of guinea pigs, 80
- Carcinoma, Bronchial, 18
- in anthracosis, 19
- Cardiac failure, Interlobar shadows in, 30
- output, 84
- Cardiologic departments in tuberculosis hospitals, 35
- Cardiopulmonary function test, 83
- Castex, M R, and Mazzei, E S Atypical spontaneous pneumothorax, 13
- , ———, ———, ———, ———, ———  
Recurrent benign spontaneous pneumothorax, 15
- , ———, ———, ———, ———, ———  
Spontaneous benign pneumothorax, 14
- Cat, Alveolar walls of, 77
- Cattaraugus County, Tuberculosis among children and young adults in, 51
- Caud, S Circulation time, 82
- Cavities, closure of, Fat transplant for, 6
- , pulmonary, Encapsulation of, 58
- , Surgical closure of, 5
- , Tuberculous, 57
- , ———, Giant, 57
- Cavity, Tuberculous, in infant of eight weeks, 53
- Cerebral tuberculosis simulating tumor, 71
- Cervical adenitis, Tuberculous, 69
- Cervicitis, Tuberculous, 70
- Changes in lungs following irradiation, 25
- Charr, R Carcinoma in anthracosis, 19
- Chest diseases, Coal miners', in Scotland, 20
- , shape of, Tuberculin reaction and, 54
- Children and young adults in Cattaraugus County, Tuberculosis among, 51
- , Atelectasis in, 52
- , Multiple cystic tuberculosis of bones in, 55
- , Pneumothorax in, 53
- , pulmonary fibrosis in, Follow-up of, 27
- , school, in rural Belgium, Incidence of tuberculous infection in, 40
- , Tuberculin reactions in, 47
- , Tuberculosis in, 50, 51
- , ———, Vitamin C in, 54
- , Tuberculous peritonitis in, 65
- , ———, Vitamin C in, 55
- with pulmonary tuberculosis, Results of collapse therapy in, 53
- Christian, H A Haemothorax in cirrhosis of liver, 35
- Christie, R V Dyspnoea, 85
- Chronic miliary tuberculosis, 56
- Circulation, pulmonary, Dual, 85
- time, 82
- , volume and, of lung, Variations in, 83
- Cirrhosis of liver, Haemothorax in, 35
- Clark, E, and Rubenfeld, S Hodgkin's disease of the lungs, 27
- Clark, G M, and Colt, G H Tuberculous disease of abdominal lymph nodes, 68
- Clerf, L H Bronchial carcinoma, 18
- Coal miners' chest diseases in Scotland, 20
- , Pneumoconiosis and tuberculosis in, 19
- Collapse measures, 3
- therapy in children with pulmonary tuberculosis, Results of, 53
- ——— results, 4
- Colt, G H, and Clark, G M Tuberculous disease of abdominal lymph nodes, 68
- Complex, primary, Exacerbation of, 53
- , ———, Progressive, 76
- Congenital cystic disease of lung, 22
- ———, Total pneumonectomy for, 22
- cysts of lung, 23

- Control of tuberculosis, 19
- Coon, H M See Gale, J W, *et al*, 22
- Cooper, D A, and Erb, W H Death following phrenicectomy, 2
- Corper, H J Tuberculous infection in guinea pigs, 80
- Corrillo, P N Tuberculous cavities, 57
- , —, —, and Hochberg, L A Thoracoplasty with pneumothorax and pleural effusion, 2
- , —, —, —, Ornstein, G G Giant tuberculous cavities, 57
- , —, —, —, Weinstein, M Subtotal scapulectomy, 6
- Coughing, Mechanism of, 86
- Course and mortality of tuberculosis in different age groups, 40
- Courville, C B, and Evans, H S Calcified tuberculoma of brain, 71
- Crozier, and Martin, E Pulmonary fibrosis in miners, 19
- Cystic bronchiectases, 8
- disease, Congenital, of lung, 22
- —, —, Total pneumonectomy for, 22
- tuberculosis, Multiple, of bones in children, 55
- Cysts, Congenital, of lung, 23
- , Lung, 23
- , Mediastinal, 33
- Dauer, C C Trends of tuberculosis mortality by sex, 41
- Death following phrenicectomy, 2
- Decline in tuberculosis mortality, 42
- Derscheid, G, and Toussaint, P Encapsulation of pulmonary cavities, 58
- Detroit, Tuberculosis prevention in, 48
- Diabetes and tuberculosis, 61
- Diabetic coma, Tuberculous meningitis resembling, 72
- Diaphragmatic hernia, 31
- —, Traumatic, 32
- Diehl, H S See Myers, J A, *et al*, 45
- Dirkse, P R, and Peirce, C B Pulmonary pneumatocele, 22
- Diseases, chest, Coal miners', in Scotland, 20
- Distribution, Bronchogenic, of fluid and particulate matter, 86
- Dual pulmonary circulation, 85
- Duodenum, oesophagus, stomach and, Pressures in, 86
- Durand, H Lung abscess, 9
- Dye, Spread of, in skin of tuberculous guinea pigs, 88
- Dyspnoea, 85
- Early pulmonary tuberculosis, 55
- Effusion, Interlobar, 31
- , pleural, pneumothorax and, Thoracoplasty with, 2
- Ellison, R T Mediastinal hernia, 32
- Empyema, Periapical, 29
- , Tuberculous, 64
- Encapsulation of pulmonary cavities, 58
- England, Prevention of tuberculosis among young adults in, 36
- Englebreth Holm, J Tuberculosis splenomegaly, 67
- Epituberculosis, 52
- Epstein, I G, and Ornstein, G G Tuberculous bronchitis, 63
- Erb, W H, and Cooper, D A Death following phrenicectomy, 2
- Erythema nodosum and pulmonary tuberculosis, 52
- Evans, H S, and Courville, C B Calcified tuberculoma of brain, 71
- Exacerbation of primary complex, 53
- Experimental tuberculous panophthalmitis, 87
- Extrathoracic, Intra- and, tuberculosis, 76
- Fat transplant for closure of cavities, 6
- Fatal haemorrhage, 76
- spontaneous pneumothorax due to ruptured bulla of lung, 13
- Feldman, W H, and Stasney, J Leucocytic response in sensitized calves, 88
- Ferrando, G, and Rabino, A Social importance of the modern sanatorium in Italy, 44
- Fetter, W Epituberculosis, 52
- Fibrosis, pulmonary, in children, Follow-up of, 27
- , —, — miners, 19
- Fineman, S Jejunum in tuberculosis, 66
- Fixation, Spinal, 75
- Fluid and particulate matter, Bronchogenic distribution of, 86

- Follow up of pulmonary fibrosis in children, 27
- Fractures of ribs, Spontaneous, in pulmonary tuberculosis, 62
- Frommelt Müller, C Tuberculosis problem in India, 49
- Frost, W H Control of tuberculosis, 19
- Function, Pulmonary, 81
- Ginschtein, L Hodgkin's disease and tuberculosis, 27
- Fusion, Spinal, in tuberculosis of spine, 75
- , —, Short bone graft for, 76
- Gale, J W, Kerley, J L, and Coon, H M Total pneumonectomy for congenital cystic disease, 22
- Gaucher's disease of lungs, 27
- Giant tuberculous cavities, 57
- Gilbert, Lilian See Lincoln, Edith M, *et al*, 47
- Goldberger, Esther See Kereszturi, Camille, *et al*, 17
- Gough, J Fatal spontaneous pneumothorax due to ruptured bulla of lung, 13
- Graham, E A See Tuttle, W M, *et al*, 1
- Gray, W A Experimental tuberculous panophthalmitis, 87
- Great Britain and South Africa, Silicosis laws in, 21
- , —, Bovine tuberculosis in humans in, 46
- Green, H Exacerbation of primary complex, 53
- Greenbaum, Evelyn, and Bullock, J G M Pneumococcus type VII pneumonia, 12
- Greger, C Skin temperatures in tuberculosis of joints, 73
- Grevle, A Hospital observation on spondylitic patients, 75
- Griffith, A S Bovine tuberculosis in humans in Great Britain, 46
- Guinea pigs, Spontaneous tuberculosis of, 80
- , —, Tuberculous infection in, 80
- , —, Spread of dye in skin of, 88
- Haberland, H O F Bone tuberculosis, 73
- Haematogenous pulmonary tuberculosis, 56
- Haemopneumothorax, Spontaneous, 16
- Haemoptysis, 57
- of uncertain cause, Bronchoscopic investigation of, 26
- Haemorrhage, Fatal, 76
- Haemothorax in cirrhosis of liver, 35
- Hall, J A M Coal miners' chest diseases in Scotland, 20
- Hamada, G Spinal fixation, 75
- Hamperl, H Benign tumors of bronchi, 17
- Harmon, G L See Vaughn, H F, *et al*, 48
- Hart, P M D'A Prevention of tuberculosis among young adults in England, 36
- Hatcher, C H, and Phemister, D B Tuberculous infection of the hip joint, 73
- Hausbrandt, F Intimal changes in branches of portal vein, 78
- Heart in pulmonary tuberculosis, 62
- Hellstadius, A Tuberculous spondylitis, 75
- Hernia, Diaphragmatic, 31
- , —, Traumatic, 32
- , Medistinal, 32
- Hertzberg, G Tuberculosis in two Norwegian forest districts, 42
- Higgins, H L, and Burgin, L B Phlyctenulosis, 71
- Himsworth, H P Diabetes and tuberculosis, 61
- Hip joint, Tuberculous infection of the, 73
- Hochberg, L A, and Coryllos, P N Thoracoplasty with pneumothorax and pleural effusion, 2
- Hodgkin's disease and tuberculosis, 27
- of the lungs, 27
- Holman, E Partial resection of lower scapula, 5
- Hopkins, H U Spontaneous haemopneumothorax, 16
- Hospital observation on spondylitic patients, 75
- personnel, Tuberculosis in, 45
- , tuberculosis, Readmissions to, 63
- workers, Canadian, Tuberculosis in, 45
- Hospitals, tuberculosis, Cardiologic departments in, 35
- Households, Periodic accrediting of, 36
- Hoyle, C Chronic miliary tuberculosis, 56
- Hsieh, C K, and Kimm, H T Changes in lungs following irradiation, 25
- Humphreys, G H, Moore, R L, Maier, H C, and Apgar, Virginia Cardiac output, 84
- Hypersensitiveness, Tuberculin, 1

- Ikeda, K Bronchomoniliasis, 6  
 Immunity, Scrofula and, in tuberculosis, 70  
 Incidence of tuberculous infection in school children in rural Belgium, 40  
 India, Tuberculosis problem in, 49  
 Industrial workers, Pneumonia and tuberculosis among, 46  
 Industry, Tuberculosis problem in, 43  
 Infant of eight weeks, Tuberculous cavity in, 53  
 Infants, Tuberculosis in, 50  
 Infarction of lung, 26  
 Infection, Bovine, 62  
 —, Tuberculous, among soldiers, 41  
 —, —, in guinea pigs, 80  
 —, —, Incidence of, in school children in rural Belgium, 40  
 —, —, of the hip joint, 73  
 Interlobar effusion, 31  
 — shadows in cardiac failure, 30  
 Intestinal tuberculosis, 66  
 Intimal changes in branches of portal vein, 78  
 Intra- and extrathoracic tuberculosis, 76  
 Irradiation, Changes in lungs following, 25  
 Ischium, Tuberculous osteitis of the, 73  
 Italy, Social importance of the modern sanatorium in, 44  
 —, Tuberculosis morbidity in, 41
- Jejunum in tuberculosis, 66  
 Jetter, W W, and Bumbalo, T S Vitamin C in tuberculosis, 55  
 —, —, —, —, —, —  
 Vitamin C in tuberculosis in children, 54  
 Johnstone, J G Treatment of joint tuberculosis, 72  
 Joint, hip, Tuberculous infection of the, 73  
 — tuberculosis, Treatment of, 72  
 Joints, tuberculosis of, Skin temperatures in, 73  
 Jonnesco, D, and Stoichitz, N N Pulmonary mycosis, 7  
 Joyner, A L, and Sabin, F R Spread of dye in skin of tuberculous guinea pigs, 88
- Kaunitz, J Atelectasis, 27  
 Kautz, F G, and Pinner, M Periapical empyema, 29  
 Kealey, J L See Gale, J W, *et al*, 22
- Kereszturi, Camille, Goldberger, Esther, and Nojima, Kimi Tuberculin allergy in the aged, 47  
 Kibbey, C H Pneumonia and tuberculosis among industrial workers, 46  
 Kimm, H T, and Hsieh, C K Changes in lungs following irradiation, 25  
 Klosk, E Fatal haemorrhage, 76  
 Kornat, M Tuberculosis in children, 51  
 Korns, J H Tuberculosis among children and young adults in Cattaraugus County, 51  
 Krafchik, L L, and Slobody, L B Tuberculous meningitis resembling diabetic coma, 72
- Lane, R E Tuberculosis problem in industry, 43  
 Lanza, G Bone marrow changes in tuberculosis, 77  
 Law, J L, and Perham, W S Multiple cystic tuberculosis of bones in children, 55  
 Leibovici, D, and Ornstein, G G Pressures in oesophagus, stomach and duodenum, 86  
 Leon, J L, and Bobrowitz, I D Readmissions to a tuberculosis hospital, 63  
 Leslie, G L, and Anderson, R S Collapse measures, 3  
 —, —, —, —, —, —  
 Collapse therapy results, 4  
 Leucocytic response in sensitized calves, 88  
 Leverton, W R Heart in pulmonary tuberculosis, 62  
 Levine, H B, and White, P D Infarction of lung, 26  
 Levitin, J Interlobar effusion, 31  
 Lincoln, Edith M, Raia, Antonette, and Gilbert, Lilian Tuberculin reactions in children, 47  
 Liver, cirrhosis of, Haemothorax in, 35  
 Lung abscess, 9  
 —, Congenital cystic disease of, 22  
 —, — cysts of, 23  
 — cysts, 23  
 — in xanthomatosis, 28  
 —, Infarction of, 26  
 —, Nitrogen metabolism in, 86  
 —, ruptured bulla of, Fatal spontaneous pneumothorax due to, 13

- Lung, tuberculosis of, Vascular changes in, 78  
 —, volume and circulation of, Variations in, 83  
 Lungs, Changes in, following irradiation, 25  
 —, Gaucher's disease of, 27  
 —, Hodgkin's disease of the, 27  
 —, Vanishing, 24  
 Lymph nodes, abdominal, Tuberculous disease of, 68
- MacIntyre, I C Tuberculosis in New Zealand, 42  
 Macklin, C C Alveolar walls of cat, 77  
 Macklin, Madge T Tuberculosis in Canadian hospital workers, 45  
 Magnusson, R Tuberculous osteitis of the ischium, 73  
 Magnússon, S Course and mortality of tuberculosis in different age groups, 40  
 Maier, H C See Humphreys, G H, *et al*, 84  
 Marfan, A B Scrofula and immunity in tuberculosis, 70  
 Marks, J H Diaphragmatic hernia, 31  
 Martin, E, and Croizier Pulmonary fibrosis in miners, 19  
 Mask, box, and face tent, Oxygen administration with, 35  
 Mast, W H, and McDonough, J P Traumatic diaphragmatic hernia, 32  
 Masugi, M, Murasawa, S, and Ya, S Aschoff bodies in tuberculous individuals, 34  
 Mazzei, E S, and Castex, M R Atypical spontaneous pneumothorax, 13  
 —, —, —, —, —, —, —, —  
 Recurrent benign spontaneous pneumothorax, 15  
 —, —, —, —, —, —, —, —  
 Spontaneous benign pneumothorax, 14  
 McDonough, J P, and Mast, W H Traumatic diaphragmatic hernia, 32  
 McGibbon, J E G, and Baker-Bates, E T Bronchoscopic investigation of haemoptysis of uncertain cause, 26  
 Mechanism of coughing, 86  
 Mediastinal cysts, 33  
 — hernia, 32  
 Meersseman, F Tuberculous infection among soldiers, 41  
 Meningitis, Tuberculous, resembling diabetic coma, 72  
 —, —, Variability of findings in, 72  
 Metabolism, Nitrogen, in lung, 86  
 Miliary tuberculosis, Chronic, 56  
 Miller, J A Unsolved problems of tuberculosis, 39  
 —, —, —, and Rappaport, I Pulmonary function, 81  
 Miller, Minam, and Wood, D A Dual pulmonary circulation, 85  
 Miners', Coal, chest diseases in Scotland, 20  
 —, —, Pneumonoconiosis and tuberculosis in, 19  
 —, Pulmonary fibrosis in, 19  
 Mitchell, Gertrude F Tuberculous pericarditis and Pick's disease, 66  
 Molner, J G See Vaughn, H F, *et al*, 48  
 Moore, G A Intestinal tuberculosis, 66  
 Moore, R L See Humphreys, G H, *et al*, 84  
 Morbidity, Tuberculosis, in Italy, 41  
 Mortality of tuberculosis in different age groups, Course and, 40  
 —, tuberculosis, Decline in, 42  
 —, —, Trends of, by sex, 41  
 Moskacheva, K A, and Reinberg, S A Lung in xanthomatosis, 28  
 Muller, E M Diabetes and tuberculosis, 61  
 Multiple cystic tuberculosis of bones in children, 55  
 Murasawa, S See Masugi, M, *et al*, 34  
 Mycosis, Pulmonary, 7  
 Myers, B Gaucher's disease of lungs, 27  
 Myers, J A, Trach, B, Diehl, H S, and Boynton, Ruth E Tuberculosis in hospital personnel, 45  
 Myerson, M C Bronchoscopy in tracheo-bronchial tuberculosis, 64
- Nayer, H R Intestinal tuberculosis, 66  
 Neubert, B Vascular changes in tuberculosis of lung, 78  
 Neuheoff, H Fat transplant for closure of cavities, 6  
 New Zealand, Tuberculosis in, 42  
 Nitrogen metabolism in lung, 86  
 Nojima, Kimi See Kereszturi, Camille, *et al*, 47  
 Norwegian forest districts, two, Tuberculosis in, 42

- Nüss, M Bovine infection, 62
- Nylin, G Cardiopulmonary function test, 83
- O'Brien, E J See Tuttle, W M, *et al*, 1
- Observation, Hospital, on spondylitic patients, 75
- Oesophagus, stomach and duodenum, Pressures in, 86
- Ornstein, G G, and Coryllos, P N Giant tuberculous cavities, 57
- , —, —, Epstein, I G Tuberculous bronchitis, 63
- , —, —, Leibovici, D Pressures in oesophagus, stomach and duodenum, 86
- Ortega, L, and Verdes Cardiologic departments in tuberculosis hospitals, 35
- Osteitis, Tuberculous, of the ischium, 73
- Oxygen administration with box mask and face tent, 35
- Panophthalmitis, tuberculous, Experimental, 87
- Parodi, F Variations in volume and circulation of lung, 83
- Partial resection of lower scapula, 5
- Particulate matter, fluid and, Bronchogenic distribution of, 86
- Peirce, C B, and Dirkse, P R Pulmonary pneumatocele, 22
- Perham, W S, and Law, J L Multiple cystic tuberculosis of bones in children, 55
- Periapical empyema, 29
- Percarditis, Tuberculous, and Pick's disease, 66
- Periodic accrediting of households, 36
- Pentomitis, Tuberculous, in children, 65
- Petter, C K Intra- and extrathoracic tuberculosis, 76
- Phemister, D B, and Hatcher, C H Tuberculous infection of the hip joint, 73
- Phlyctenulosis, 71
- Phrenicectomy, Death following, 2
- Pick's disease, Tuberculous pericarditis and, 66
- Pinner, M, and Kautz, F G Periapical empyema, 29
- Pleural effusion, pneumothorax and, Thoracoplasty with, 2
- Pneumatocele, Pulmonary, 22
- Pneumococcus pneumonia, 12
- type-VII pneumonia, 12
- Pneumonectomy, Total, for congenital cystic disease, 22
- Pneumonia and tuberculosis among industrial workers, 46
- , Pneumococcus, 12
- , — type-VII, 12
- Pneumonoconiosis and tuberculosis in coal miners, 19
- Pneumothorax and pleural effusion, Thoracoplasty with, 2
- , benign, Spontaneous, 14
- in children, 53
- , spontaneous, Atypical, 13
- , —, benign, Recurrent, 15
- , —, Fatal, due to ruptured bulla of lung, 13
- Portal vein, Intimal changes in branches of, 78
- Pregnancy and tuberculosis, 63
- Pressures in oesophagus, stomach and duodenum, 86
- Prevention of tuberculosis among young adults in England, 36
- , Tuberculosis, in Detroit, 48
- Price, D Tuberculosis in infants, 50
- , — Tuberculous cavity in infant of eight weeks, 53
- Primary complex, Exacerbation of, 53
- —, Progressive, 76
- Prognosis in tuberculosis of tonsils and adenoids, 68
- Progressive primary complex, 76
- Pseudocavitation, 25
- Pulmonary cavities, Encapsulation of, 58
- circulation, Dual, 85
- fibrosis in children, Follow-up of, 27
- — — miners, 19
- function, 81
- mycosis, 7
- pneumatocele, 22
- tuberculosis, children with, Results of collapse therapy in, 53
- —, Early, 55
- —, Erythema nodosum and, 52
- —, Haematogenous, 56
- —, Heart in, 62
- —, Spontaneous fractures of ribs in, 62
- —, Stenosis of large bronchi in, 62



- Rabino, A, and Ferrando, G Social importance of the modern sanatorium in Italy, 44
- Rabinowitz, L, and Rogers, E J Lung cysts, 23
- Rais, Antoinette See Lincoln, Edith M, *et al*, 47
- Rappaport, I, and Miller, J A Pulmonary function, 81
- Raven, M O Follow-up of pulmonary fibrosis in children, 27
- Reaction, Tuberculin, and shape of chest, 54
- Reactions, Tuberculin, in children, 47
- Readmissions to a tuberculosis hospital, 63
- Recurrent benign spontaneous pneumothorax, 15
- Reichle, H S Bronchogenic distribution of fluid and particulate matter, 86
- Reid, B, and Wilkinson, M C Tuberculous cervical adenitis, 69
- Reinberg, S A, and Moskacheva, K A Lung in xanthomatosis, 28
- Reisner, D, and Tchertkoff, I G Cystic bronchiectases, 8
- Resection, Partial, of lower scapula, 5
- Results, Collapse therapy, 4
- of collapse therapy in children with pulmonary tuberculosis, 53
- Ribs, Spontaneous fractures of, in pulmonary tuberculosis, 62
- Rogers, E J, and Rabinowitz, L Lung cysts, 23
- Rosenblüth, M B, and Block, M Pneumococcus pneumonia, 12
- Roubier, C Interlobar shadows in cardiac failure, 30
- Rubenfeld, S, and Clark, E Hodgkin's disease of the lungs, 27
- Rural Belgium, Incidence of tuberculous infection in school children in, 40
- Rykels, D K Decline in tuberculosis mortality, 42
- Sabbione, C Spontaneous fractures of ribs in pulmonary tuberculosis, 62
- Sabin, I R, and Joyner, A L Spread of dye in skin of tuberculous guinea pigs, 88
- Sacro iliac tuberculosis, 74
- Saenz, A, and Cannetti, G Spontaneous tuberculosis of guinea pigs, 80
- Sanatorium, modern, Social importance of the, in Italy, 44
- Sandler, E Stenosis of large bronchi in pulmonary tuberculosis, 62
- Scapula, lower, Partial resection of, 5
- Scapulectomy, Subtotal, 6
- Schenck, S G Congenital cysts of lung, 23
- Schumann, C Pseudocavitation, 25
- Scotland, Coal miners' chest diseases in, 20
- Scrofula and immunity in tuberculosis, 70
- Sellers, T H Surgical closure of cavities, 5
- Sen, P K Pneumonococcosis and tuberculosis in coal miners, 19
- Sensitized calves, Leucocytic response in, 88
- Sex, Trends of tuberculosis mortality by, 41
- Shadows, Interlobar, in cardiac failure, 30
- Short bone graft for spinal fusion, 76
- Siegal, M, and Singer, B Results of collapse therapy in children with pulmonary tuberculosis, 53
- Silicosis laws in Great Britain and South Africa, 21
- Singer, B, and Siegal, M Results of collapse therapy in children with pulmonary tuberculosis, 53
- , —, — Van Bark, B Vitamin C in tuberculous children, 55
- Skillen, Jane, and Bogen, E Pregnancy and tuberculosis, 63
- Skin of tuberculous guinea pigs, Spread of dye in, 88
- temperatures in tuberculosis of joints, 73
- Slobody, L B, and Krafchik, L L Tuberculous meningitis resembling diabetic coma, 72
- Social importance of the modern sanatorium in Italy, 44
- Soldiers, Tuberculous infection among, 41
- South Africa, Great Britain and, Silicosis laws in, 21
- Spencer, J, and Warren, S Boeck's sarcoid, 80
- Spinal fixation, 75
- fusion in tuberculosis of spine, 75
- —, Short bone graft for, 76
- Spine, tuberculosis of, Spinal fusion in, 75
- Splenomegaly, Tuberculosis, 67
- Spondylitic patients, Hospital observation on, 75

- Spondylitis, Tuberculous, 75
- Spontaneous benign pneumothorax, 14
- fractures of ribs in pulmonary tuberculosis, 62
- haemopneumothorax, 16
- pneumothorax, Atypical, 13
- —, benign, Recurrent, 15
- —, Fatal, due to ruptured bulla of lung, 13
- tuberculosis of guinea pigs, 80
- Spread of dye in skin of tuberculous guinea pigs, 88
- Stasney, J, and Feldman, W H Leucocytic response in sensitized calves, 88
- Stenosis of large bronchi in pulmonary tuberculosis, 62
- Stevenson, C S Tuberculous cervicitis, 70
- Stewart, C A Periodic accrediting of households, 36
- Stoichitza, N N, and Jonnesco, D Pulmonary mycosis, 7
- Stomach, oesophagus, and duodenum, Pressures in, 86
- Subtotal scapulectomy, 6
- Surgical closure of cavities, 5
- Sutherland, D P Aspects of the tuberculosis problem, 47
- Swift, W E Spinal fusion in tuberculosis of spine, 75
- Tchertkoff, I G, and Reisner, D Cystic bronchiectases, 8
- Temperatures, Skin, in tuberculosis of joints, 73
- Tent, face, box mask and, Oxygen administration with, 35
- Test, Cardiopulmonary function, 83
- Thelander, H E, and Baldwin, Janet Variability of findings in tuberculous meningitis, 72
- Therapy, collapse, in children with pulmonary tuberculosis, Results of, 53
- , —, results, 4
- Thompson, F Sacro iliac tuberculosis, 74
- Thoracoplasty with pneumothorax and pleural effusion, 2
- Tonsils and adenoids, tuberculosis of, Prognosis in, 68
- Total pneumonectomy for congenital cystic disease, 22
- Toussaint, P, and Derscheid, G Encapsulation of pulmonary cavities, 58
- Trach, B See Myers, J A, *et al*, 45
- Tracheobronchial tuberculosis, Bronchoscopy in, 64
- Transplant, Fat, for closure of cavities, 6
- Traumatic diaphragmatic hernia, 32
- Treatment of joint tuberculosis, 72
- Trends of tuberculosis mortality by sex, 41
- Tuberculin allergy in the aged, 47
- hypersensitiveness, 1
- reaction and shape of chest, 54
- reactions in children, 47
- Tuberculoma of brain, Calcified, 71
- Tuberculosis among children and young adults in Cattaraugus County, 51
- , Bone, 73
- , — marrow changes in, 77
- , Bovine, in humans in Great Britain, 46
- , Cerebral, simulating tumor, 71
- , Control of, 49
- , cystic, Multiple, of bones in children, 55
- , Diabetes and, 61
- , Hodgkin's disease and, 27
- hospital, Readmissions to a, 63
- hospitals, Cardiologic departments in, 35
- in Canadian hospital workers, 45
- — children, 50, 51
- — —, Vitamin C in, 54
- — coal miners, Pneumoconiosis and, 19
- — different age groups, Course and mortality of, 40
- — hospital personnel, 45
- — infants, 50
- — New Zealand, 42
- — two Norwegian forest districts, 42
- , Intestinal, 66
- , Intra- and extrathoracic, 76
- , Jejunum in, 66
- , joint, Treatment of, 72
- , miliary, Chronic, 56
- morbidity in Italy, 41
- mortality, Decline in, 42
- —, Trends of, by sex, 41
- of joints, Skin temperatures in, 73
- — lung, Vascular changes in, 78
- — spine, Spinal fusion in, 75

- Tuberculosis of tonsils and adenoids, Prognosis in, 68
- , Pneumonia and, among industrial workers, 46
- , Pregnancy and, 63
- , prevention in Detroit, 48
- , —, of, among young adults in England, 36
- , problem, Aspects of the, 47
- , —, in India, 49
- , —, —, industry, 43
- , pulmonary, children with, Results of collapse therapy in, 53
- , —, Early, 55
- , —, Erythema nodosum and, 52
- , —, Haematogenous, 56
- , —, Heart in, 62
- , —, Spontaneous fractures of ribs in, 62
- , —, Stenosis of large bronchi in, 62
- , Sacro iliac, 74
- , Scrofula and immunity in, 70
- , splenomegaly, 67
- , Spontaneous, of guinea pigs, 80
- , tracheobronchial, Bronchoscopy in, 64
- , Unsolved problems of, 39
- , Vitamin C in, 55
- Tuberculous bronchitis, 63
- , cavities, 57
- , —, Giant, 57
- , cavity in infant of eight weeks, 53
- , cervical adenitis, 69
- , cervicitis, 70
- , children, Vitamin C in, 55
- , disease of abdominal lymph nodes, 68
- , empyema, 64
- , guinea pigs, Spread of dye in skin of, 88
- , individuals, Aschoff bodies in, 34
- , infection among soldiers, 41
- , —, in guinea pigs, 80
- , —, Incidence of, in school children in rural Belgium, 40
- , —, of the hip joint, 73
- , meningitis resembling diabetic coma, 72
- , —, Variability of findings in, 72
- , osteitis of the ischium, 73
- , panophthalmitis, Experimental, 87
- , pericarditis and Pick's disease, 66
- , peritonitis in children, 65
- , spondylitis, 75
- Tumor, Cerebral tuberculosis simulating, 71
- Tumors, Benign, of bronchi, 17
- Tuttle, W M, O'Brien, E J, and Graham, E A Tuberculin hypersensitiveness, 1
- Unsolved problems of tuberculosis, 39
- Urechia, C Cerebral tuberculosis simulating tumor, 71
- Van Antwerp, L D Tuberculous peritonitis in children, 65
- Van Bark, B, and Singer, B Vitamin C in tuberculous children, 55
- van den Eeckhout, H Incidence of tuberculous infection in school children in rural Belgium, 40
- Van Otterloo, J De Mol Short bone graft for spinal fusion, 76
- Vanishing lungs, 24
- Variability of findings in tuberculous meningitis, 72
- Variations in volume and circulation of lung, 83
- Vascular changes in tuberculosis of lung, 78
- Vaughn, H F, Harmon, G E, and Molner, J G Tuberculosis prevention in Detroit, 48
- Vein, portal, Intimal changes in branches of, 78
- Verdes, and Ortega, L Cardiologic departments in tuberculosis hospitals, 35
- Viethen, A Tuberculosis in children, 50
- Vital capacity, 81
- Vitamin C in tuberculosis, 55
- , —, —, —, in children, 54
- , —, —, —, tuberculous children, 55
- Volume and circulation of lung, Variations in, 83
- Wallgren, A Erythema nodosum and pulmonary tuberculosis, 52
- Walter-Regensburg, E Haemoptysis, 57
- Warren, S, and Spencer, J Boeck's sarcoid, 80
- Weber, H H Mechanism of coughing, 86
- Weinstein, M, and Coryllos, P N Subtotal scapulectomy, 6
- Weisman, S A Tuberculin reaction and shape of chest, 54
- White, P D, and Levine, H B Infarction of lung, 26

- |   |   |
|---|---|
| Wilkinson, M C, and Reid, B Tuberculous cervical adenitis, 69 | Xanthomatosis, Lung in, 28                          |
| Wood, D A, and Miller, Minam Dual pulmonary circulation, 85   | Ya, S See Masugi, M, <i>et al</i> , 34              |
| Wood, H G Congenital cystic disease of lung, 22               | Zavod, W A Haematogenous pulmonary tuberculosis, 56 |
| Woodruff, W Tuberculous empyema, 64                           | Zeyland, J Atelectasis in children, 52              |



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# CONTENTS ORIGINAL ARTICLES

NUMBER 1, JANUARY, 1939

The Effect of Tuberculosis on the Serological Reactions for Syphilis THOMAS PARRAN AND KENNETH LEMERSON	1
Pulmonary Tuberculosis in Young Adults WILLARD B. SOPER AND J. BURNS ANDERSON, JR.	9
Collapse Therapy in Pulmonary Tuberculosis. HOWARD W. BOS- WORTH AND C. RICHARD SMITH	33
Tuberculous Tracheobronchitis J. LAWRENCE H. HAWKINS, JR.	46
Pleural Effusion FRANCIS B. TUDHAL	57
Tuberculin Anergy in Cases with Pulmonary Calcifications PAUL D. CLARK AND DARWIN M. SHOPT	64
Variations in Leucocytes MILTON H. ANDERMAN	70
Results of Intensive Study of Sputum in Pulmonary Tuberculosis HENRY STUART WHITE AND RUBY G. KEHLA	81
Tubercle Bacilli in Sputum EMIL BOGEM AND EDWIN S. BENNETT	89
Pathology and Pathogenesis of Pulmonary Arterial Aneurysm in Tuberculous Cavities OSCAR AUERNACH	99
Virulence of Tubercle Bacilli KENNETH C. SMITHBURN	116
The Multiple Puncture Method of BCG Vaccination SOI ROY ROSENTHAL	128
Editorial—Biological Abstracts MAX PINNER	135
Books	136

NUMBER 2, FEBRUARY, 1939

Late Results of Thoracoplasty IRANI S. DOLLEY, JOHN C. JONES AND JOHN R. PAXTON	145
Intrepleural Pneumonolysis by the Closed Method RALPH C. MATSON	162
Asynchrony of the Movement of the Lower Ribs following Paralysis of the Hemidiaphragm JEROME R. HIAD	169
Chlorine for the Induction of Artificial Pneumothorax K. S. RAY, N. N. SIN AND H. N. DASGUPTA	172
Precordial Friction Rub in Spontaneous Pneumothorax MILTON R. LOUFIA	176
Protamine Insulin and Collapse Therapy in Diabetes Complicated by Pulmonary Tuberculosis BENJAMIN J. ELWOOD	181

Noncaseating Tuberculosis	RALPH HORTON, N STANLEY LINCOLN AND MAX PINNER	186
Sectional Roentgenography of the Chest	CLARENCE J ZINTHEO, JR	204
Extrapulmonary Complications of Pulmonary Tuberculosis	DAVID PERLA AND S B BILLER	215
Proteinase and Peptidase Activity of Polymorphonuclear Leucocytes, Monocytes and Epithelioid Cells of Inflammatory Exudates	CHARLES WEISS	228
Primary Infection in Adults	J ARTHUR MYERS, PHILIP T Y CH'IU AND THEODORE L STREUKENS, JR	232
The Pathology of Primary Tuberculous Infection in the Adult	HENRY C SWEANY	236
Case-Finding	ROBERT E PLUNKETT	256
Coccidioides Infection	O J FARNESS AND CHARLES W MILLS	266

## NUMBER 3, MARCH, 1939

Blastomycosis	I A Review of the Literature DONALD S MARTIN AND DAVID T SMITH	275
Climatic and Socio-Economic Factors in Mortality from Pulmonary Tuberculosis	I M MORIYAMA AND L P HERRINGTON	305
Treatment of Tuberculosis by Tuberculin Desensitization	HENRY STUART WILLIS AND T R JO CZ	318
Bronchial Catheterization	I ELLIS RUDMAN	329
Paravertebral Aspiration of Tuberculous Psoas Abscess	FREDERICK C WARRING, JR AND EDWARD M KENT	338
Factors of Healing, Latency and Progression in Pulmonary Tuberculosis	HENRY C SWEANY	348
Resistance to Tuberculosis I Factors Associated with the Bacteria	KENNETH C SMITHBURN	371
Resistance to Tuberculosis II Variations Dependent on the Age of the Host and upon Resistance Induced by Vaccination	KENNETH C SMITHBURN	383
The Demonstration of Tubercle Bacilli by Culture and by Guinea Pig Inoculation	ALBERT GUGGENHEIM AND MAX FINKELSTEIN	397
Tuberculosis Survey in Florida	ARTHUR J LOGIE	408

## NUMBER 4, APRIL, 1939

Industrial Dusts and the Mortality from Pulmonary Disease	A J LANZA AND R J VANE	419
Tuberculous Lesions in Male Industrial Workers	DONALD E CUMMINGS, ROBERT N DOWNS AND MELVIN BERG	439

Tuberculosis Control in Industry	W A SAWYER	456
Surgical Treatment of Tumors of Lung and Mediastinum	FRANK S DOLLEY AND JOHN C JONES	479
Blastomycosis II A Report of Thirteen New Cases	DONALD S MARTIN AND DAVID T SMITH	488
The Roentgenological Anatomy of the Chest	CARLETON B PEIRCE AND BRUCE W STOCKING	516
Pneumoperitoneum in the Treatment of Pulmonary Tuberculosis	HAROLD GUYON TRIMBIE, J LLOYD EATON AND GERTRUDE MOORE	528
Accidental Pneumoperitoneum	L R GAITÁN	537
Cultural Methods in the Diagnosis of Tuberculosis	HUGH G WHITLIE AD	540
Editorial—Tuberculin Anergy and the Variability of Tuberculins.	LEMOND R LONG	551

## NUMBER 5, MAY, 1939

Haematogenous Tuberculosis in the Adult	ELI H RUBIN	557
Life Expectancy in Tuberculosis	EMIL BOGÉN	587
Case Fatality Rates in Tuberculosis	GODIAS J DROLET	597
Tuberculosis Mortality in Industrial Populations of Massachusetts and Michigan	C C DAUER	603
Routine Bronchoscopy in Patients with Active Pulmonary Tuberculosis	R B McINDOR, JOHN D SIFFER, PAUL C SAMSON, R S ANDERSON AND G L LESELL	617
Diagnostic Bronchoscopy in Occult Tuberculosis	SIDNEY J SHIPMAN	629
Postmortem Incidence of Tuberculous Tracheobronchitis	I J FLANCL AND P A WHELIFF	633
Tuberculous Tracheitis	WALTER I WERNER	637
Serial Leucocyte Counts	BENJAMIN J ELWOOD AND THOMAS DE CECIO	641
Olive Oil in Pneumothorax	SPENCER SCHWARTZ AND FRED H HEISE	651
Tuberculin Survey	A E KELLER AND R H KAMPMEIER	657
An X-ray Study of the Adult Relief Population of a Small Community	D O N LINDBERG	666
The Incidence of Tuberculous Infection in Student Nurses	RUTH E BOYNTON	671
Spontaneously Acquired Tuberculosis in Rhesus Monkeys	KENNETH C SMITHBURN	675

## NUMBER 6, JUNE, 1939

Pulmonary Tuberculosis in the Second Decade of Life I Its Development and Fatality	DAVID ZACKS	683
Pulmonary Tuberculosis in the Second Decade of Life. II. Its Treatment and Prognosis.	DAVID ZACKS	703
Diabetes and Pulmonary Tuberculosis	HOWARD F ROOT AND WALTER R BLOOR	714
Oral Tuberculosis	JAMES CLUTE BRYANT	738
Bilateral Tuberculous Pleurisy with Effusion	GEORGE C WILSON	745
Erythrocyte Sedimentation	THOMAS DE CECIO AND BENJAMIN J ELWOOD	748
The Epidemiological Aspects of the Negative Tuberculin Reaction	M PARETZKY	754
The Detection of Tuberculosis in Group Surveys	PHILLIP T KNIES	766
Tuberculosis Survey of an Entire Community	ROBERTS DAVIES AND C A SCHERER	778
The Effects of Ultraviolet Radiation on Tubercle Bacilli	KENNETH C SMITHBURN AND GEORGE I LAVIN	782
Vitamin C and Immunity in Tuberculosis of Guinea Pigs	FRED H HEISE AND WILLIAM STEENKEN, JR	794
Pathological Changes in Pulmonary Tuberculosis among Jamaican Negroes	C W WELLS	796
Case Reports		
Anthracosilicosis Simulating Pulmonary Carcinoma	HOWARD H BRADSHAW AND RICHARD J CHODOFF	817
An Unusual Case of Tuberculosis of the Spine	THEODORE T FOX, MICHAEL S BURMAN AND SAMUEL SINBERG	825

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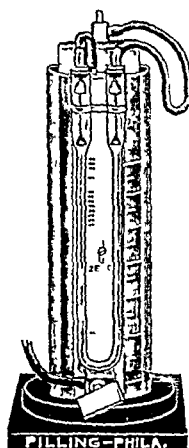
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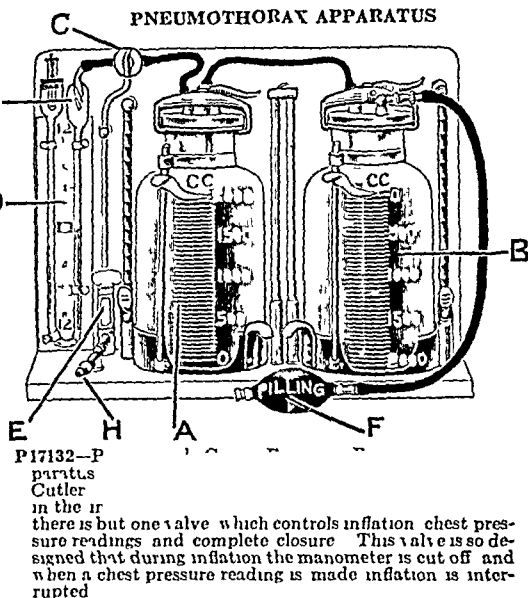
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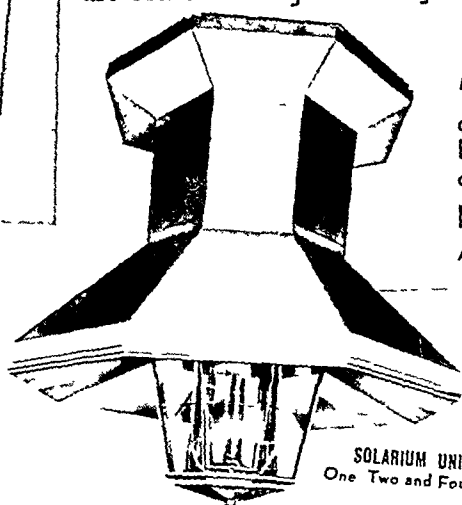
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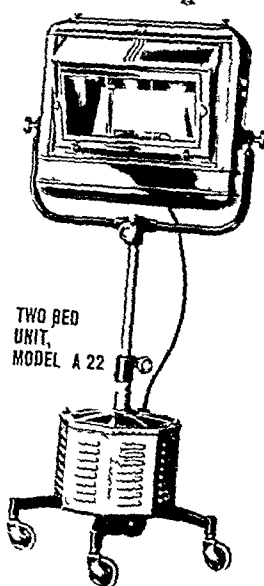
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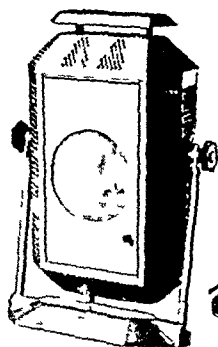
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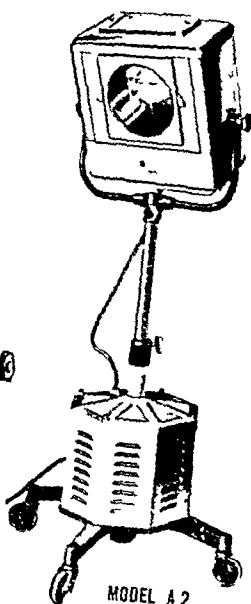
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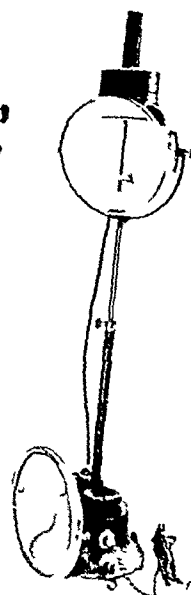
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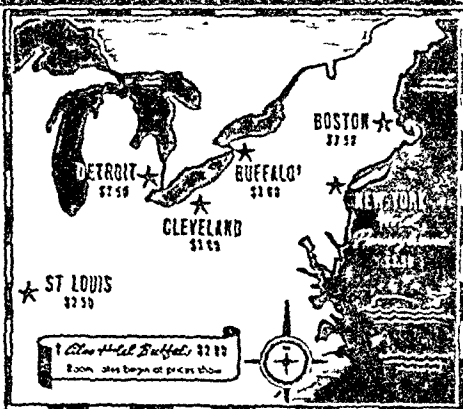


- BALION HARRY C    Physiological Mechanism of Expectora-  
tion
- GEARY, PAUL    Extrapleural Pneumothorax
- CUTLER J W    Phrenic Nerve Interruption
- RIST, ARTHUR    Reestablishment of Pneumothorax
- SIMPSON, HOWARD L    Fatality Rates in Pulmonary Tuber-  
culosis
- WIDVAIN, WILLIAM H, AND CAMPBELL, HUGH B    Laryngeal  
Tuberculosis
- COHN, MAURICE L    Preservation of Tubercle Bacilli
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*The Table of Contents for the  
 September issue will be selected  
 from the following articles*

BRONFENBRENNER, J The Allergic  
 State and Its Relation to Hyper-  
 sensitiveness and Resistance

APPEL, J M, DOUGLAS, B H, JOCZ,  
 T R, AND WILLIS, H S Rela-  
 tion between Tuberculin Allergy  
 and Clinical Course

STEELE, ARTHUR H, AND WILLIS,  
 HENRY STUART The Applica-  
 tion of the Newer Purified Tu-  
 berculin Products by the Pirquet  
 Method

PARETZKY, M The Diagnostic Ap-  
 plication of High Doses of Tu-  
 berculin

DOUGLAS, BRUCE H, AND VAUGHAN,  
 HENRY F A New Administra-  
 tive Technique in Tuberculosis  
 Case-Finding

WELLS, C W Tuberculosis in Con-  
 tacts of Children Who React to  
 Tuberculin

BRAILEY, MIRIAM Factors Influenc-  
 ing the Course of Tuberculous  
 Infection in Young Children

MYERS, J ARTHUR The Latent or  
 Smouldering Stages in Tubercu-  
 losis

MOORMAN, LEWIS J Multiple Cal-  
 cifications in the Spleen

DUNCAN, G R, AND MARIETTE, E S  
 An Evaluation of Artificial Hy-  
 perpyrexia in Tuberculosis

ELRICK, LEROY Mediastinal Hernia  
 Following Massive Atelectasis

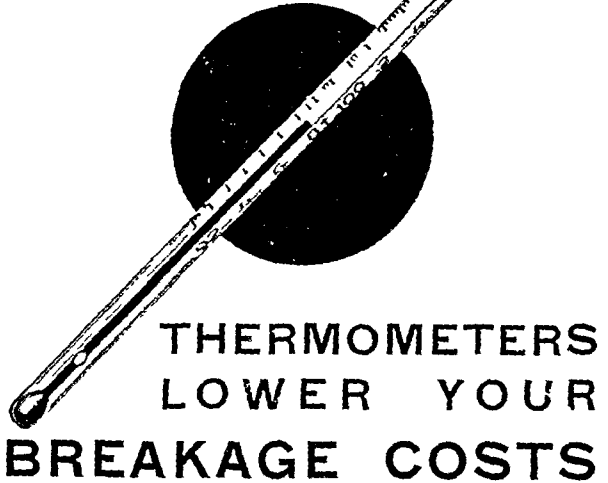
SHAMASKIN, ARNOLD, AND ROGOFI,  
 JACOB Reinduction of Pneumo-  
 thorax

VOORSANGER, WILLIAM C Artificial  
 Pneumothorax Reestablished  
 after Phrenicovagotomy

SKOLNICK, MAX H Trauma as a  
 Factor in Pott's Disease

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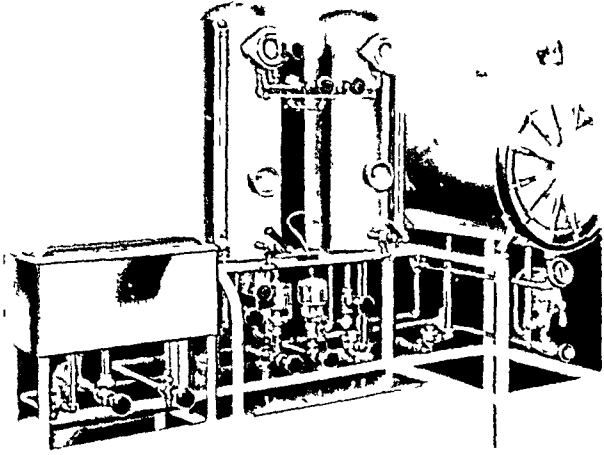
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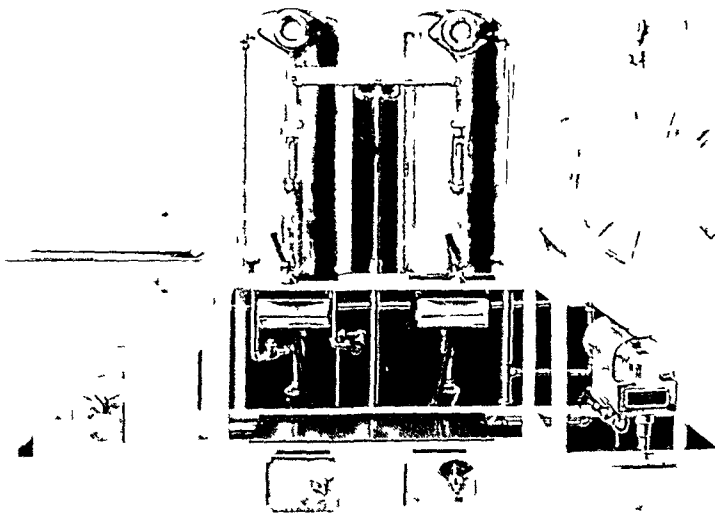
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# CONTENTS

MCDONALD, E. B. AND CRAWFORD, J. H. Tomography With Special Reference to Its Value in the Diagnosis of Pulmonary Lesions	163
NOSSE, JOS. L. AND KAHN, MORTON C. Experimental Tuberculosis Infection in the Endothelium and the Mechanism of Its Spread	191
RYAN, W. J. AND MEDLER, T. M. Coexistence of Lymphocytic Leukemia and Late-Advanced Pulmonary Tuberculosis	212
SPENCE, MORRIS GUYNE, MEDFORD R. AND KEAMEY, BENJAMIN The Effect of Vitamin A Deficiency on Experimental Tuberculosis in the Guinea Pig and Rabbit	222
MASSEN, A. R. The Sedimentation Rate and Medlar's Index	239
HANAN, EUSTACE B. AND LITCH, WALTER P. Precipitation of Water Soluble Tuberculo-Protein by Hydrogen Ion Concentration	244
BANAY, ANDREW L. Topical Application of Codliver Oil in Tuberculosis	250
KOTOL, ELLIOT M. Purified in Pulmonary Emphysema	259
LOVE, EUGEN N. The Relation of Intrapleural Pressures to the Formation of Effusions in Artificial Pneumothorax	263
JACOBS, M. AND BLOCH, H. M. Intrathoracic Treatment of Tuberculous Cavities	268
BUCHANAN, OSCAR A. Acetic Solution in the Treatment of Pulmonary Haemorrhage	276
FRANK, LORENZ W. Tuberculous Peritonitis	279
BEATTY, OLIVER A. Manifestations of Undulant Fever in the Respiratory Tract	283
Editorial: Kenyon Dunham	290
Abstracts of Tuberculosis	1

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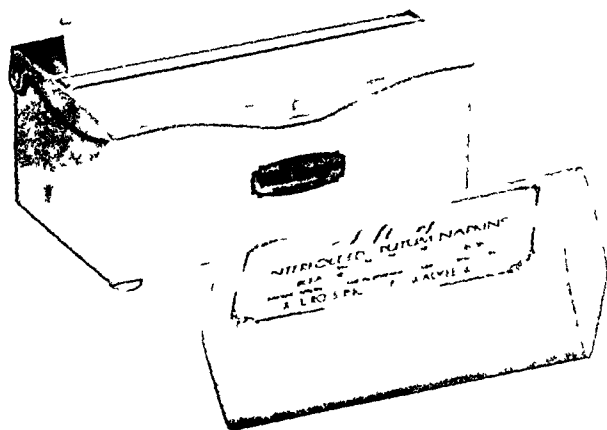
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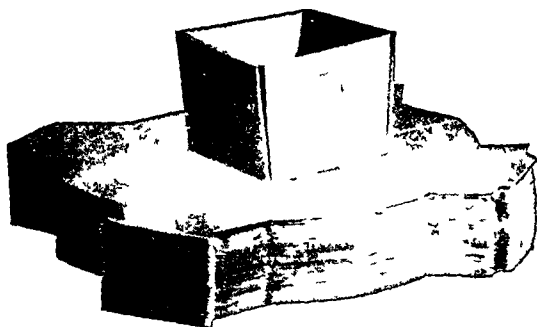
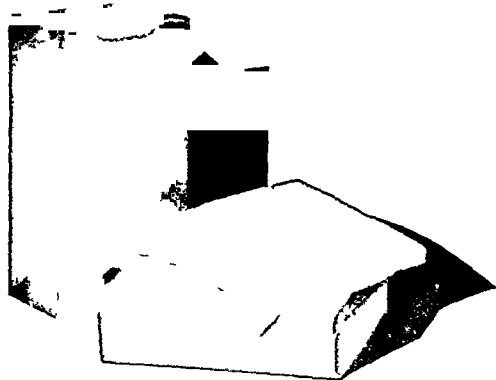
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# TOMOGRAPHY

With Special Reference to Its Value in the Diagnosis of Pulmonary Lesions

J B McDOUGALL<sup>1</sup> AND J H CRAWFORD<sup>2</sup>

## 1 INTRODUCTION

The concept of radiology has widened considerably since the discovery of X-rays by Roentgen in 1895, and the advances made in this subject have been no less than in other branches of medicine and science during this period. The services rendered by radiology to the art of diagnosis are paralleled only by those of anaesthetics and antiseptics for treatment, so much so, that it is impossible to visualise modern medicine, as we know it, without this acquired aid.

Alban Kohler, in the preface to the most recent edition of his monumental book, enumerates twenty subdivisions of the field of radiology, ranging from amniography to venography which he had been compelled to omit from his volume—a striking indication of the remarkable increase in the extent and technique of modern roentgenology. Almost every organ of the body has been brought within the scope of the radiologist, and the advances which have been made in the reproduction of even the finest detail of soft tissues are eloquent testimony to the success of workers in this field.

The particular problem of the chest has always been of some difficulty owing to the presence of the bony structures forming the thoracic cage, and it was as a contribution to the solution of this problem that tomography, that is, the reproduction of layers of the chest, was devised.

## 2 THEORY OF TOMOGRAPHY

### *1 Sources of difficulty in the interpretation of a skiagram of the chest*

In radiology it is well known that there may occur a diminution in the translucency of normal lung tissue by reason of thick scapulae, well-formed pectoral muscles, the mammary gland in females, or a large thymus gland in children. More important than any of these factors,

<sup>1</sup> Medical Director, Preston Hall Sanatorium, Kent, England

<sup>2</sup> Assistant Medical Director, Preston Hall Sanatorium

however, is the presence of the ribs, the shadow of which covers about two-thirds of the lungs. This simple fact is not often appreciated. Thus we have a translucent organ, the lung, encircled by much less translucent parts, not only do difficulties of superimposition arise, but for adequate penetration harder rays must be used than those which would be suitable for the lungs themselves.

Further difficulties in the interpretation of the ordinary anteroposterior film of the chest are due to the superimposition of the structures within the lung itself. Shadows of blood-vessels, bronchioles and alveoli are

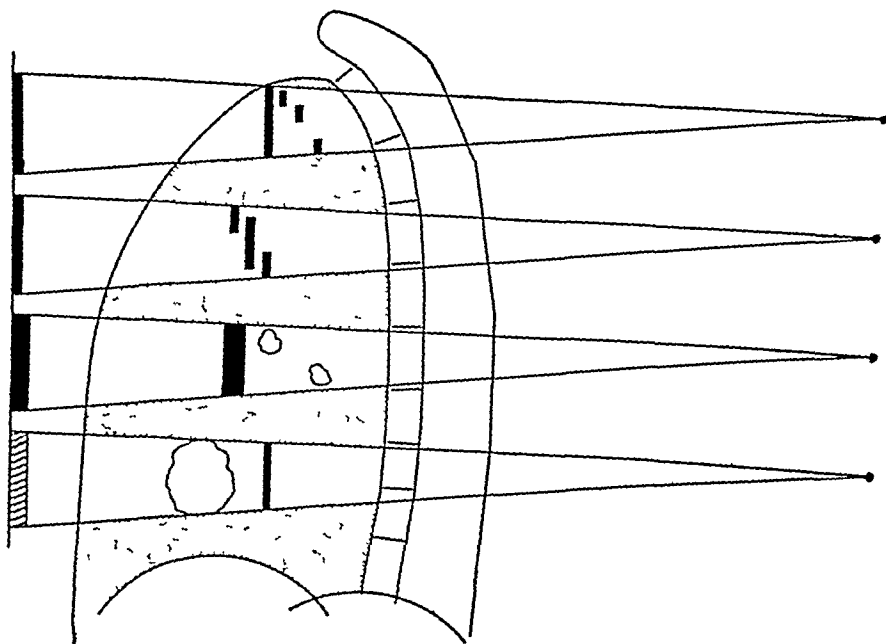


Fig 1 Showing superimposition of lesions

superimposed, and give rise to sharp contrasts which may be wrongly interpreted as being due to pathological lesions. When one recalls that the usual "flat" film of the chest is simply the product of the shadows of all the structures which lie within the effective cone of rays during the exposure, it becomes evident that the analysis and interpretation of the final picture may often be difficult, and, in some cases, even misleading.

Figure 1 (adapted from Chaoul) gives a simple illustration of the superimposition of foci situated at different depths in the chest, small lesions or structures which lie in the path of the shadow cast by a large, dense

lesion are entirely covered and lost, and in this way it is possible for the shadow of a cavity, for example, to be quite obliterated. Any method, therefore, whereby layers of the chest at previously determined depths can be photographed places at our disposal the means for exact representation of pulmonary lesions, with a consequent gain in accuracy of diagnosis. And as far back as 1921, Bocage attempted, with only limited success, to produce an apparatus which would satisfy these requirements and reproduce a lung-section free from superimposed shadows.

*2 Advantages of tomography over stereoscopy* Before going on to a discussion of the geometrical principles of tomography, it may be of value to consider the question of stereoscopy as an aid toward the elucidation of intrapulmonary lesions. We will readily admit that by the use of oblique films, or stereoscopic films, the expert radiologist is often able to obtain a greater degree of differentiation than is possible with the usual dorsoventral picture, but, even so, free and isolated vision of different foci is only produced to a limited degree. Furthermore, the fact that a large number of people cannot see stereoscopically limits its practical value and militates against its wide adoption. The fact has to be recognized that, despite many attempts to stimulate and maintain interest in stereoscopic work, this method of investigation has never been very widely adopted, and it is our experience that tomography reveals with clarity lesions which are difficult to demonstrate by the other methods enumerated above.

*3 Geometrical principles of tomography* The fundamental idea of photographing sections of the body, as introduced by Bocage, is to coordinate the motion of the tube and the film around an object which remains fixed during the exposure. Objects on the particular plane which is in focus are thus constantly projected on the same point of the film, while objects lying in any other plane (not in focus) throw their shadows on different points of the film, as a result of this continuous movement or "wandering," effacement of the shadows is produced. The greater the distance of these points from the cross-section in focus, the greater is the degree of their erasure.

Figure 2 shows how this takes place.  $T_1$  and  $T_2$  represent the initial and final positions of the tube during the exposure. In the initial position  $T_1$ , the image of the object,  $a-b$ , is projected to  $a_1-b_1$  on the film, in the final position  $T_2$ , the image is projected to  $a_2-b_2$ , but in the time



that the tube has moved from  $T_1$  to  $T_2$ , the film has moved from position 1 to position 2, and thus the image of  $a-b$  falls on the *same* two points of the film. On the other hand, the point  $P$ , lying in a plane which is not in focus, is projected to *different* points on the film during the synchronized movement of the plate and the tube, and thus at no time is it exposed for a sufficiently long period to produce an image.

Starting from the geometrical proof of this idea, Bocage believed that the longer and the more complete he could make the excursion of the tube,

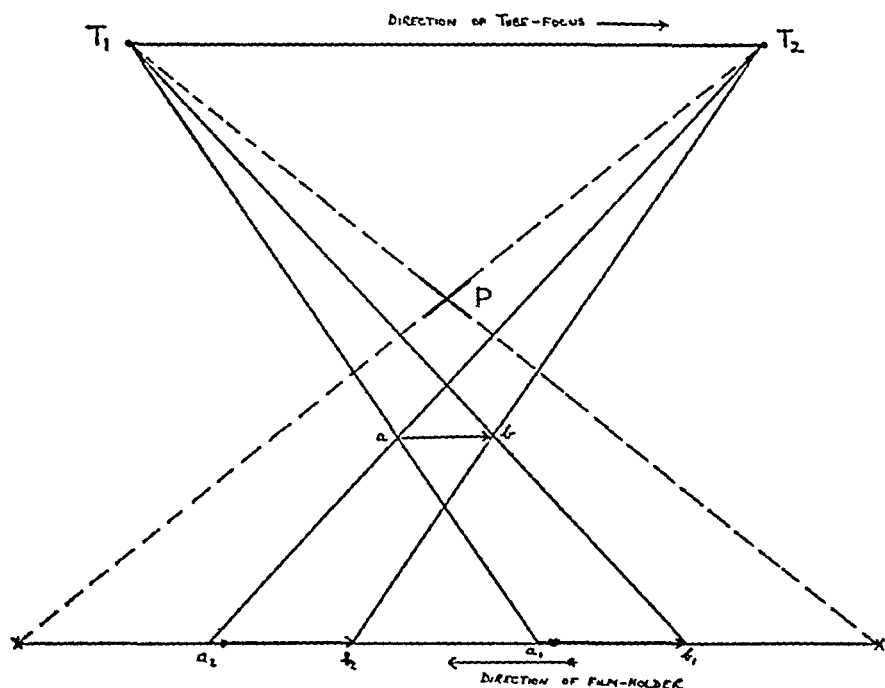


Fig 2 Illustrating the principle of tomography showing "wandering" of points not in focus

the more effective would be the effacement of shadows of objects above and below the particular section to be reproduced. In this he was followed by later workers in this field, particularly Bartelink and Vallebona, who, as a result of a mistaken geometrical approach to the problem, suggested that the tube should move along an Archimedean spiral (Bocage), a sinus line (Bartelink), or some other type of curve which as nearly as possible would produce effacement of unwanted shadows. But such a motion, that is, around one axis, is only adequate for the representation of small fields, for the photography of a large area, movement around two axes becomes necessary.

With such methods of moving the tube the apparatus becomes increasingly complicated, and long exposures were found to be necessary. Furthermore, difficulties arose with the Potter-Bucky diaphragm as a result of which the film became partially shaded by the grid elements of the diaphragm. The loss of time in exposure caused by these diaphragm shadows could only be avoided by imparting a complicated motion to the diaphragm, similar to that described by the tube, and the final result was that the apparatus they elaborated was hardly practicable for routine X-ray work and consequently failed to be adopted.

### 3. DESCRIPTION OF PRESENT APPARATUS

In the modern tomograph apparatus, constructed in 1935 to the plans of Grossman and Chaoul of the X-ray department of the Charité University Clinic of Berlin, the motion of the tube has been considerably simplified and the use of a diaphragm made possible.

Figure 3 is a photograph of the apparatus, showing the tube in the initial position of the pendulum. The machine, as manufactured by the Sanitas Electrical Company of Berlin, and as used by us, consists essentially of a two-armed pendulum oscillating about a horizontal axis. To the upper and longer arm, which is above the table, is attached a supporting lever for the tube. To the lower and shorter arm, below the table, is attached a rectangular holder which contains the Potter-Bucky diaphragm and the film-holder. The tube-container may be moved both vertically and horizontally. The difficulties with the diaphragm in the early types of apparatus noted in the preceding section are avoided by moving the tube in a plane perpendicular to the layer to be radiographed. This is achieved by arranging that the plane of the middle-grid element coincides with the plane in which the focus is moved. The pendulum itself is fixed to a block, which is suspended between a stand of two posts in such a way that the block can be moved up and down and fixed in any desired position. Above the tube, and attached to it, is a pulley system running on an arc. The fixation block contains a graduated scale by means of which the extent of the swing of the tube is controlled. The pendulum is pulled over to the initial position at one end of the arc by releasing a pin in the centre of the block.

### 4. TECHNIQUE OF EXAMINATION

*1: Procedure:* Tomographic investigation should only be used after having completed the routine radiological examination of the patient by

means of screening and the usual X-ray photograph. The depth of the patient's chest is measured in full inspiration and the calculations are

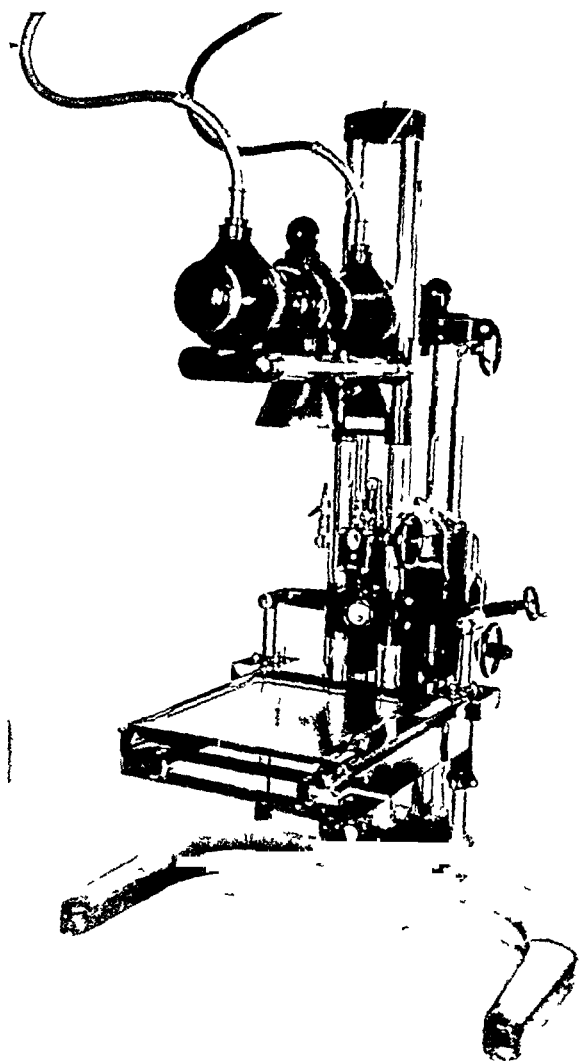


Fig. 3 The tomograph

made for the sections of the chest required. It is at once apparent that the number of sections which may be reproduced is limited only by the depth of the patient's chest, but the question had to be settled, not least

from the point of view of economy and the time at one's disposal, as to the number of tomograms to be taken in each case to provide adequate diagnostic information. Following the practice of Chaoul, we take three photographs, as follows, as a routine in each case:

1. *Ventral*, that is, about 7 cm. from the front of the chest-wall
2. *Medial*, that is, about midway between the front and the back, this usually corresponds approximately to the level of the hilum of the lung
3. *Dorsal*, that is, about 7 cm. from the back

Should the distribution of the lesion be such that it is advisable to take further sections, it is our practice to take premedian, predorsal and post-dorsal photographs at depths of 2 cm. in front of or behind the corresponding main sections enumerated above. It is only rarely, however, that as many sections as this have to be taken to establish the site and distribution of the lesion.

The distances required for the three standard sections having been obtained, the tube is adjusted to the required height and then swung over to the initial position at one end of the arc. The cassette is placed in position on the film-holder, the diaphragm is set, and the machine is then ready to take the required photograph.

*2 Position of the patient* The position of the patient varies according to the photograph to be taken. For an ordinary frontal cross-section of the chest, the tube should move in a direction parallel to the body axis, thus the patient lies in the long axis of the table. In the case of lateral sections, the direction of the tube must be transverse to the body, this is achieved by having the patient lying across the table. The importance of this lies in the fact, first pointed out by Grossman, that the tomograph gives blurring in one direction, and, to overcome this, it is necessary to move the tube in a direction perpendicular to the direction of the shadows. This requirement is satisfied by adjusting the position of the patient in the manner described above.

*3 Exposure and technical considerations* The time of exposure is usually one second for taking section photographs. This may appear to be a long period, but experience has shown that it is with this time of exposure that the best results are obtained. The voltage and strength of the current are varied for the different sections to be taken. For ordinary frontal sections, a 6-kilowatt tube is ample, but for lateral sec-

tions a 10-kw tube is necessary. The optimum voltage and current for the frontal sections is 60-65 kv with 70-150 ma, working at a distance 0.90 to 1.50 metres between the section and the film. For lateral photographs, voltages between 80-90 kv are used with a current of 150 ma, the time of exposure being the same.

Voltage and strength of current may be altered in different cases according to the thickness of the patient and the density of the lesions.

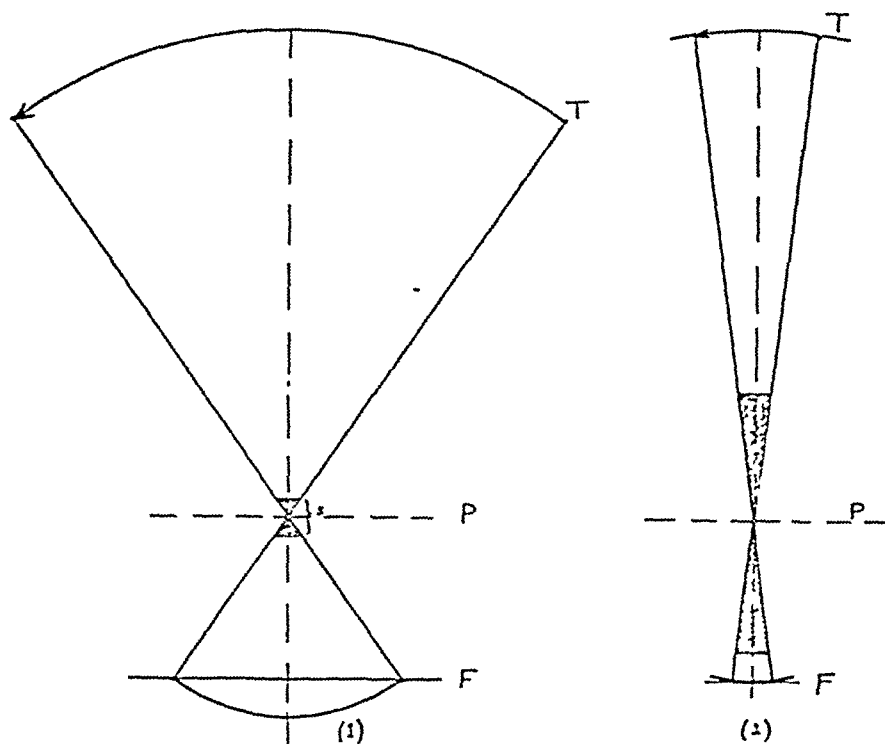


Fig. 4 To show relationship between width of section and angle of elongation

*4 Width of section.* In the apparatus of Bocage, the stratum of the body which was photographed was extremely thin and was really of little value from the point of view of diagnosis. Chaoul has modified this in the apparatus described above, and, as a result, a stratum of any desired thickness may be reproduced. Actually, the thickness of the cross-section varies with the extent of the arc described by the tube,—the greater the arc the thinner is the layer, and the smaller the arc the thicker is the layer—so that when the arc is at its minimum (that is, nil), and

the tube does not swing at all but remains at rest, the section which is then reproduced comprises the entire thickness of the chest and is really not a 'section' at all. That is to say, the tomograph apparatus is then being used as an ordinary radiographic machine and thus takes the usual X-ray photograph of the chest

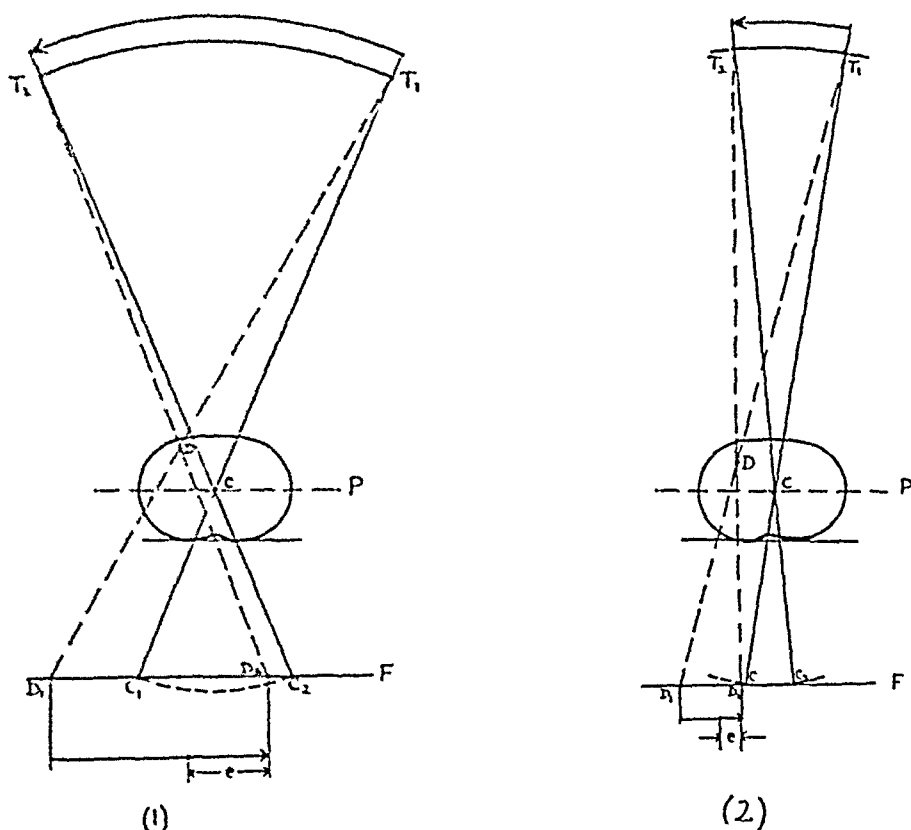


Fig 5 To show relationship between degree of erasure and angle of elongation

Figure 4 is a geometrical representation of the proof that the thickness of the section depends upon the angle of the arc described by the tube. The plane P represents the section in focus, T is the path of the tube, and F the position of the film, with S as the thickness of the section. The variation in S is clearly brought out in positions 1 and 2. The degree of effacement of unwanted shadows, and consequently the clarity of definition of the picture, is also dependent upon the angle of elongation, as is shown in figure 5.

Position 1 shows the projection of a point D which is above the section in focus, to determine the degree of effacement of this point, the distance  $C_1-C_2$  (representing the projection of an object in the centre of the plane, on to the centre of the film) is subtracted from the distance  $D_1-D_2$ , and is given by E in the diagram. In position 2, where the angle of elongation is diminished, the degree of erasure is much less.

## 5 TOMOGRAPHY OF THE NORMAL LUNG

*1 Anatomical introduction* Before discussing the appearance of layers of a normal lung, as revealed by the tomograph, it will be of value to describe the anatomical distribution of the pulmonary vessels and the bronchial tree.

(a) *The pulmonary arteries* According to Gray's *Anatomy* (23rd edition), the pulmonary artery is about 5 cm in length and 3 cm in diameter, and arises from the conus arteriosus of the right ventricle. It then runs upward and backward, passing at first in front and then to the left of the ascending aorta to the level of the fibrocartilage between the 5th and 6th thoracic vertebrae, where it divides into right and left branches of nearly equal size.

The *right* branch runs horizontally behind the ascending aorta and superior vena cava, but in front of the right bronchus to the root of the right lung, where, according to W. Felix, it lies between the eparterial and the hyparterial bronchi, it then proceeds to divide into three branches, as follows:

- (i) Two branches to the upper lobe, running in front of the eparterial bronchus.
- (ii) One branch, the main one, to supply the middle and lower lobes, this runs underneath the hyparterial bronchus.

Even the further ramifications of these vessels have a certain degree of regularity, despite individual variations, and it is possible to identify the following peripheral distribution in the right lung:

- (i) In the upper lobe, three vessels, namely, ventral, apical and dorsal branches.
- (ii) In the middle lobe, three vessels, namely, one dorsal and two ventral.
- (iii) In the lower lobe, three superficial branches (ventral, median and dorsal), and one deep branch descending along the mediastinum.

The *left* pulmonary artery runs horizontally in front of the descending aorta and the left main bronchus to the root of the left lung, where it divides into two main branches for each lobe of the lung. Here again,

the larger vessel is the branch to the lower lobe. The peripheral distribution to the lobes of the left lung is as follows (after Greineder)

- (i) In the upper lobe, five branches may be traced, namely, dorsal, apical and ventral branches, and two branches to the lingula
- (ii) In the lower lobe, three superficial branches, namely, dorsal, apical and ventral, and one deep branch descending along the mediastinum

The description given above, in which each lobe has a principal vessel dividing into several branches, is true for the great majority of cases, but a so-called aberrant type has been described in which the lobes are supplied by several branches entering them at different points

(b) *The pulmonary veins* These are four in number, two from each lung, and are formed by the joining together of venules coming from the capillary network on the walls of the alveoli of the lungs. One vessel is formed from each lobule of the lung, and these vessels, uniting successively, form a single trunk from each lobe, three from the right lung and two from the left, the vein from the middle lobe of the right lung generally unites with that from the upper lobe, so that ultimately two veins, a superior and an inferior, leave each lung, but occasionally the three veins on the right side remain separate. At the root of the lung, the superior pulmonary vein lies ventrally, in front of, and a little below, the pulmonary artery and the main bronchus, the inferior is situated at the lowest part of the hilum and on a plane posterior to that of the superior vein. It is only in the internal portion of the lungs that the veins accompany the arteries and bronchi, toward the surface of the lungs the veins pursue a separate course and run in the connective tissue septa between the small lobuli, while the arteries ramify in the actual centre of the lobule

(c) *The bronchi* The bifurcation of the trachea into the two bronchi occurs at the level of the upper border of the 5th thoracic vertebra

The right bronchus is wider, shorter and more vertical than the left, and is about 2.5 cm long, entering the right lung nearly opposite the 5th thoracic vertebra. The azygos vein arches over it from behind, while the right pulmonary artery lies at first below and then in front of it. The peculiarity of the right bronchus is that it gives off an eparterial branch, so called because it arises above the right pulmonary artery, it supplies the upper lobe of the right lung. The continuation of the



main bronchus is known as the hyparterial branch this passes below the artery and divides into two branches for the middle and lower lobes of the lung respectively

The *left* bronchus is narrower but longer than the right, being nearly 5 cm long, and enters the hilum of the left lung opposite the 6th thoracic vertebra, passing beneath the arch of the aorta. The left pulmonary artery lies at first above and then in front of it, there is no eparterial branch to the left bronchus

2 *Description of a tomogram of a normal lung* Figure 6 is a tomogram of the lung of a normal healthy adult, taken through the level of the hilum, that is, a median section. The first feature which will be noted



Fig 6 Tomograph of normal lung

is the absence of the rib-shadows over the lung area, it is only at the lateral margin of the thorax that small parts of the ribs are visible where they have been cut by the section

The lung field appears as a uniform background traversed by the radiating pulmonary structures coming from the lung root. It will be observed that the tomogram, in comparison with the usual type of skiagram of the chest, gives a slight loss in definition, but this is not of such a degree as to detract from its value in diagnosis. The cardiac shadow shows no material difference from that seen on an ordinary X-ray, except that its transverse diameter is clearly greater on the ventral photograph than on the dorsal by reason of its anatomical situation. The trachea, however, shows up with considerable clarity as a transparent strip running down to its bifurcation, and the bronchial divisions

may be traced to their peripheral ramifications, the main bronchi, in contrast to the pulmonary vessels, show up as transparent structures

On the right side the eparterial and hyparterial divisions of the bronchi may be identified, with the shadow of the pulmonary artery between, and the continuation of this vessel to the lower lobe can be followed. Accompanying this branch is the bronchus to the lower lobe, and on the medial side of this, between it and the cardiac margin, is the shadow of the vein running to the lower lobe. In a dorsal-section photograph, the deep descending branch of the pulmonary artery may be identified close to the mediastinum. In the upper lobe, the various branches of the artery may be clearly seen two running in a vertical direction to the apex and one more or less transversely.

On the left side again the distribution of the vessels may be followed without difficulty. In this film, an interesting feature is the presence of a small calcified lymph node in the right upper zone, with a second one at the hilum.

Greiner has published a series of lateral tomograms of the normal lung which are of particular value in showing the relations of the structures at the hilum. Considerable care is required, however, in the interpretation of these pictures, but certainly structures which normally are never or at best only indistinctly seen are revealed with astonishing clarity.

## 6 TOMOGRAPHY IN PULMONARY LESIONS

*1 The analysis of gross disease* In discussing the value and significance of tomography in pulmonary cases, we shall begin with two cases in which the ordinary dorsoventral skiagram revealed a gross lesion which normally would have been considered to portray a certain pathological process, but which, in fact, entirely failed to give an accurate representation of the exact nature and distribution of the lesion. The ordinary skiagram was not lacking in technical efficiency, but, because it can only show a summation of all the shadows coming within the area of the rays, it necessarily failed to give an exact conception of the disease. It is true that those physicians and radiologists who regularly adhere to Osler's dictum, and follow up their cases to the postmortem table, are soon made aware of the considerable degree of disease that remains unrevealed by the X-ray machine, but it is only too common to find the belief that the X-ray picture is infallible, and the final arbiter of the patient's destiny. And if tomography will serve only to demonstrate the wealth of

disease which may lie unsuspected, and thus to provide a useful corrective to our former opinions, it will have served its purpose

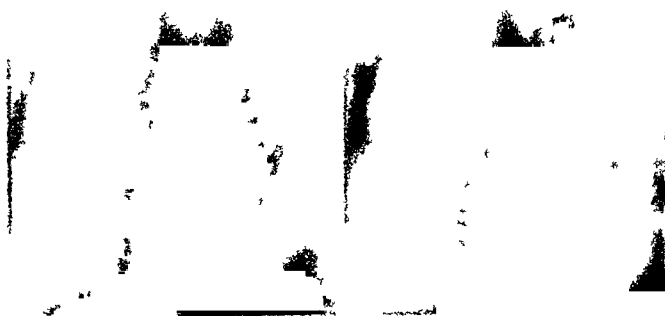
*Case 1* Figures 7a, b, c and d give a series of films of a patient, S A B, admitted to Preston Hall Sanatorium

Figure 7a is the usual dorsoventral skiagram taken on admission. The *right* lung shows an extensive diffuse lesion involving the upper and mid zones, and appears to be of a highly active type, there is, however, no definite indication of cavity-formation. The *left* lung reveals a large cavity in the upper lobe, with two stout fibrous bands traversing the lower portion of the cavity, over the remainder of the lung there is extensive infiltration with the characteristic "fluffy" appearance of exudative disease.

Figure 7b is a ventral tomogram of the same case, taken 7 cm from the front of the chest. It will be observed how clearly the trachea is revealed, even the larynx standing out with extreme clarity, and both the thyroid cartilage and the cricoid cartilage are easily identified, together with the narrowing produced by the vocal cords. On the original plate (though not, perhaps, on the reproduction shown here) the actual serrations produced on the internal surface of the trachea by the tracheal cartilages may be made out without difficulty. Taking the lung fields, we find the lesion on the *right* side to consist, at this level, of discrete, scattered nodules over all zones, but most dense at the apex. Otherwise, there is nothing definite to be noted in this lung. On the *left* side, the cavity is seen to be occupying almost the whole of the upper lobe ascending to the very apex, but the fibrous bands of the first film do not appear, the lower lobe is now seen to contain a large, irregular cavity at the base and adherent to the diaphragm, and above this are several smaller cavities, none of which were apparent on the first film.

Figure 7c is a reproduction of the median tomogram, taken midway between the front and the back of the chest. The trachea is now seen to be pulled over to the left side, and, lower down, the division into the two bronchi may be seen, the hyparterial bronchus on the right showing up particularly well, together with its continuation into the substance of the lung. The *right* lung now shows the genesis of a cavity-system in the upper lobe, with several scattered acinous nodules in the mid zone, the pulmonary artery is seen as an opaque mass between the eparterial and hyparterial bronchi. On the *left* side, the origin of the fibrous bands may just be seen at the base of the cavity, which remains very large and

about the same time that  
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house of the Lord, and the  
people of the Lord were  
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es 8a, b, c, d, e, f and g are reproductions of the tomograms of F P , a patient admitted for treatment at Preston. Whereas in the preceding case the standard fourorsoventral, ventral, median, and dorsal, were taken as discussed, in this case we have taken a larger series of many interesting features revealed by the standard group in the first instance, and also to illustrate the method of successive sections

In the usual skiagram of the chest, reading this film, one can see that the *right* lung contains old-standing fibrotic disease of the upper zones below the clavicle. One close to the mediastinum toward the lateral margin of the lung, in addition, the *right* lung appears to have a knuckle of fibrous tissue within its lumen. There is an area of recent infiltration which appears on the *right* leaf of the diaphragm is peaked and adherent, with the costophrenic angle. The *left* lung shows infiltration over the upper and mid zones, with two cavities in the lower lobe, the lower lobe appears free from disease but somewhat, and the left leaf of the diaphragm is sharply

that of the ventral tomogram taken at the usual 7 cm

The *right* lung shows a scattered area of patchy consolidation (?) over the upper and mid zones, in the lower lobe, a well-defined cavity, but no cavities are visible in the *right* leaf of the diaphragm shows one adhesion, but is outlined. Over the *left* lung, there is infiltration of an involving the upper and mid zones, but nothing more shows up clearly, and is seen to be central in position within

shows the premedian section, at a depth of 9 cm from the further 2 cm behind the preceding section. There is to be noted on the *right* side, both the scattered consolidation in the lower-lobe cavity showing up more clearly. But

Confirmation of these findings has since been obtained in this case



I<sub>15</sub> 81

I<sub>15</sub> 8b

I<sub>15</sub> 8c

I<sub>15</sub> 8d

I<sub>15</sub> 8e

I<sub>15</sub> 8f

I<sub>15</sub> 8g

I<sub>15</sub> 8a, b, c, d, e, f & g, C sec 2 for description see text

on the *left* side, the vague infiltration is now being replaced by definite shadows suggestive of cavitation in the upper and mid zones. An interesting feature is the presence of a triangular area of fibrous tissue at the level of the hilum of the lung.

Turning to the next section shown in figure 8d which is midway between the front and the back of the chest (11 cm from the front and a further 2 cm deep to the previous section) the first point to be noted is the clarity with which the trachea is revealed. The actual bifurcation, with the right and left bronchi and their subdivisions, may be easily traced. The *right* lung, in this section shows considerable differences from the previous photographs, the thickening of the upper interlobar septum is now visible, with prolongations of fibrous tissue to the periphery, and, in addition, an air space is now present in the upper lobe which is suggestive of cavitation, in the lower lobe the small cavity previously noted has now disappeared, and its place is taken by an area of diffuse infiltration. In the *left* lung the cavities in the upper lobe are now better defined, and the sharp knuckle of fibrous tissue above the pulmonary artery is very prominent.

Figure 8e is a tomogram of the predorsal section, taken a further 2 cm deep to the preceding level, and now only 9 cm from the back of the chest. The trachea and portions of the bronchi are still clearly seen, while over the *right* lung the air space in the upper lobe is increasingly well defined, in addition, a cavity is coming into view close to the mediastinum, but the infiltration in the lower lobe is fading. In the *left* lung, a cavity which was previously not visible is now coming into view in the lower mid zone.

Continuing a further 2 cm into the chest we have the dorsal section, shown on figure 8f, which is 7 cm from the back. On the *right* side, two air loculi are now apparent over the upper and middle lobes divided by a band of fibrous tissue about the level of the interlobar septum. The appearances are strongly suggestive of a localized spontaneous pneumothorax. Close to the mediastinum, in the inner part of the upper lobe, there is now a well-defined cavity, whilst over the lower lobe diffuse infiltration is now visible with the multiple adhesions to the diaphragm which were visible on the dorsoventral picture (figure 8a). On the *left* side the cavities in the upper lobe are fading, their place being taken by fibrous tissue, the cavity in the mid zone is now very well defined.

The final picture, taken as a postdorsal section, 5 cm from the skin of the back of the chest, is shown on figure 8g. The air-space in the *right*

lesion previously noted is now even more sharply defined, otherwise, the film appears as in the previous section except that the infiltration over the *left* clavicle has now broken down in parts with the resultant formation of a cavity system. The *left* lung shows no material difference, except that the mid zone cavity stands out very sharply.

It is no exaggeration to say that it is quite impossible to deduce the exact pathological state of the lesion from a study of the ordinary film. And the existence of the spontaneous pneumothorax must have remained unsuspected. The manner in which one series of cavities comes into view as another group begins to fade illustrates in the clearest manner the topography of the lesion. In broad outline the series also shows how the spicules are situated in the deeper portions of the lung tissue. This feature is brought out by our remaining cases. Pulmonary tuberculous lesions usually begin at the back of the lungs and extend by advancement to enter into the anterior sections. Hence it may often occur that the ventral tomograms are quite free from disease while the dorsal section may show old standing chronic disease.

2. *The Cavitary Lesion (Case 3)*. This case is described as an example of the value of the tomograph in revealing cavities the existence of which might not be even suspected. The previous cases have illustrated the value of tomography in *detecting* as it were a gross lesion. It might be proved that the two cases already described revealed disease in which the presence of cavities might at least have been inferred on the ordinary films without actually identifying their walls. In particular might this be said of case 1. But in the following example we feel that no amount of hypothetical conjecture could have exposed the areas of cavitation which were revealed by the tomograph.

Figure 9a is the X-ray picture of the chest in the case of D. Q. There is well marked fibrosis of the upper and mid zones of both lungs, and below the left clavicle is a chronic cavity. No other areas of cavitation are revealed. Figures 9b, c and d are reproductions of the ventral, median and dorsal tomograms respectively. In the ventral section an area of disease in the *left* mid zone may be seen with a shadow suggestive of breaking down lung tissue, on the *right* side one or two calcified lymph nodes are visible but there is no infiltration as yet. The median section shows a startling difference, apart from the clarity with which the eparterial and hyparterial divisions are revealed, there has now come into



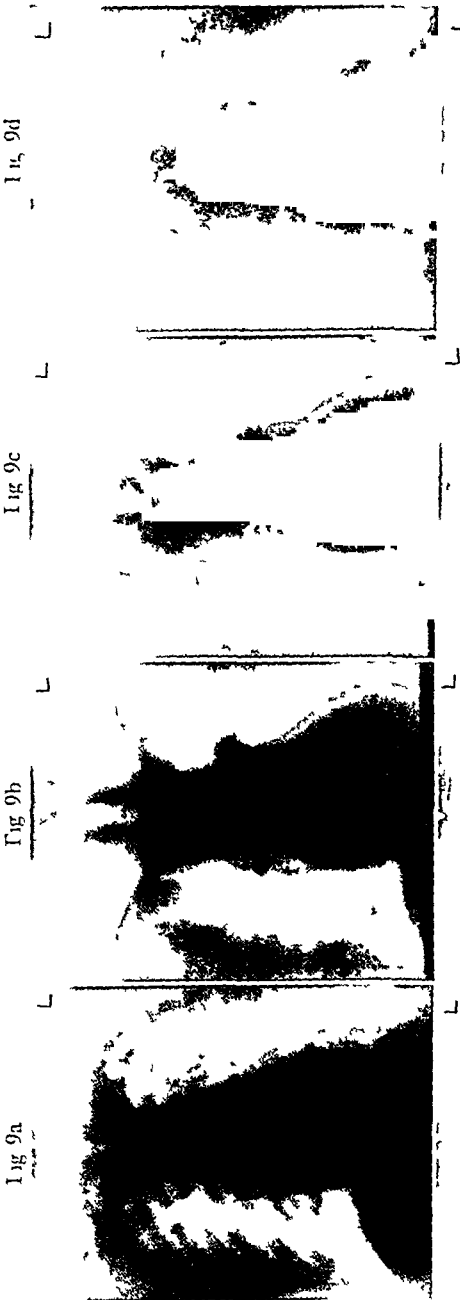


Fig 10a  
Fig 10b  
Fig 10c  
Fig 10d  
Figs 9a, b, c & d Case 3 I or description see text  
Figs 10a, b, c & d Case 4 I or description see text

view a thick walled cavity in the apical portion of the *right* middle lobe, with an area of fairly dense infiltration in the upper lobe. On the *left* side, the previously noted shadow in the mid zone is now clearly a cavity, and in addition there are now shadows over the upper zone which suggest cavitation. This is confirmed in the dorsal tomogram, where the left upper lobe cavity is sharply defined.

Thus the actual lesion consists of (1) multiple cavities in the upper lobe of the left lung situated medially and dorsally, and (2) cavitation in the middle lobe of the right lung at about the depth of the hilum.

5. *The localization of cavities*—Two cases will now be described illustrating the precise localization of a cavity which was visible on the ordinary anteroposterior film of the chest.

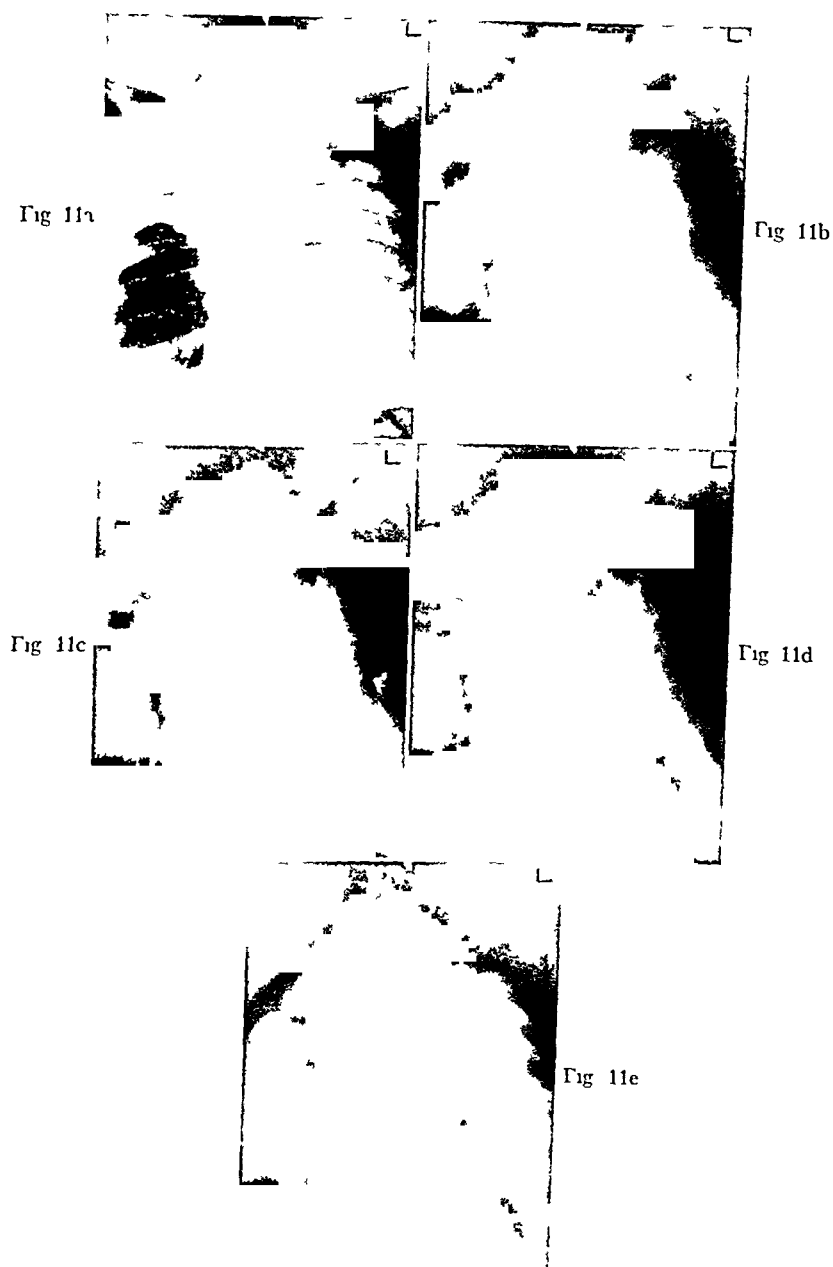
*Case 4*—Figures 10a, b, c and d are reproductions of a series of films in the case of I. A. L., the first of these shows a large thick-walled cavity below the clavicle on the *right* side. But the tomogram of the ventral section reveals the lung to be as yet quite free from disease, the median section also fails to reveal any infiltration. The dorsal section, however, shows the large cavity to be present and also confirms the absence of disease in the other lung.

Following this finding a successful apicolysis with posterior *plombierung* was performed.

*Case 5*—The next case is described because of the interesting localization of the cavity which is revealed by the tomograph, in addition to the exact localization of its site. Figure 11a is that of the ordinary skiagram of the chest: a large chronic thick-walled cavity is present in the *right* upper lobe with considerable thickening of the interlobar septum below, there is also some chronic fibrosis of the *left* apex. The ventral section, shown on figure 11b, reveals the thickening of the septum to be already present, with shadows of two cavities in the *right* upper lobe coming into view, note also a bronchus near the hilum sharply defined in cross-section.

The median section (figure 11c) reveals a "double cavity" system with a stout fibrous band between, furthermore, the two divisions of the cparterial bronchus can just be seen to enter the outer wall of the joint cavity system.<sup>4</sup>

<sup>4</sup> The reproduction of the films can never hope to reveal the various points with that accuracy and clarity of detail which is seen on the original tomograms.



Figs 11a, b, c, d & e Case 5 For description see text

The dorsal section (figure 11d) illustrates how these two cavities in the right upper lobe have now fused, with the resultant formation of a very large single cavity, a peculiar thickening of the inferior margin of this cavity may also be noted. We have observed a similar occurrence on a number of occasions—sometimes associated with an actual protuberance into the lumen of the cavity—while these probably represent an area of proliferation of fibrous tissue—we would not like to be dogmatic as to their exact pathological interpretation—and mention them simply as having been observed.

By the time we reach the postdorsal section, shown on figure 11e, the large cavity has however almost completely faded, thus establishing that the main distribution of the lesion in this case is really medially and slightly posteriorly.

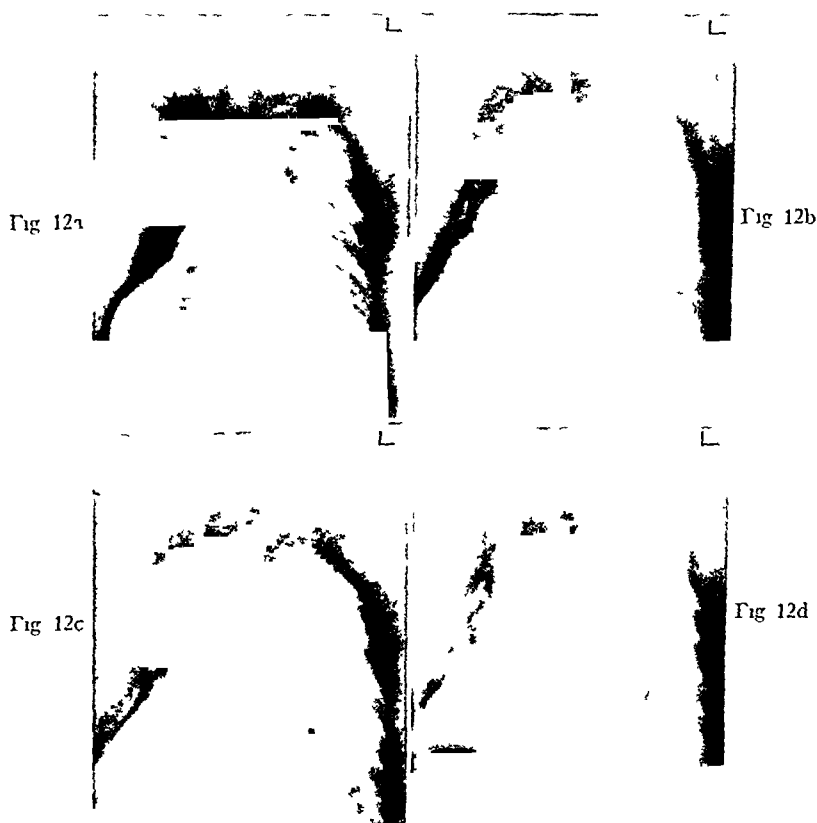
*4 Tomography in cases following thoracoplasty* There is little need for us at this stage to stress the difficulties in ordinary radiological examination of cases following extensive thoracic operations, such as a complete paravertebral thoracoplasty. In order to penetrate the dense fibrosis which occurs after the operation, a degree of penetration has to be used which leads to a "blackening" effect of the contralateral side, and the basis of comparison with the nonoperated side is seriously interfered with. Some have suggested the use of lead plates to be held over the normal lung, while the operated side is subjected to an extra exposure in order to penetrate the dense structures.

Tomography surmounts this difficulty and is therefore of especial value in such cases, indeed, it is in the investigation of this type of case that tomography has been widely used in the clinic of Professor Sauerbruch in Berlin, and the next case to be described in this series will be that of a patient who had undergone a thoracoplasty but still had a positive sputum some time after the operation.

*Case 6* The patient, R. S., had been sent to Preston Hall for investigation. Figure 12a is a reproduction of the dorsoventral film of his chest, a paravertebral thoracoplasty has been performed of the upper 7 ribs, with an excellent resultant collapse of the right upper lobe, no cavity or definite area of disease is present which might account for the persistence of the positive sputum.

The ventral film revealed nothing of note, and is not reproduced here, but the median, predorsal and dorsal sections, shown in figures 12b,

c and d, respectively indicate, first, the genesis of an area of infiltration in the right lower lobe below the operated area, then a more definite shadow strongly suggestive of early cavity-formation, and finally, the gradual disappearance of this shadow. That this was the area of disease giving rise to the positive sputum was further supported by the physical signs over this portion of the chest, and the two taken together left little doubt that this was the further focus of infection.



Figs 12a, b, c, & d Case 6 For description see text

5 *On the zone of collapse in artificial pneumothorax* Cases of artificial pneumothorax provide some of the most interesting material for tomographic investigation. Not only can the extent of the pneumothorax be easily demonstrated, but also the site and the nature of adhesions, and the case to be described is typical of many which we have examined by this means.

Fig 13a



Fig 13b



Fig 13c

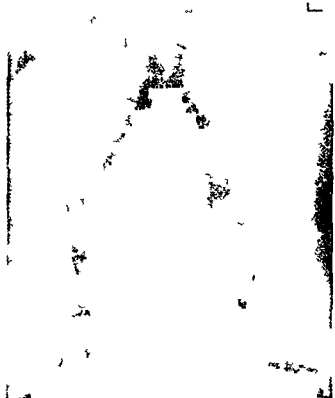


Fig 13d



Fig 13e



Figs 13a, b, c, d &amp; e Case 7 For description see text

*Case 7* Figures 13a, b, c, d and e represent a series of films in the case of L S, who was admitted for treatment with an extensive lesion of the right lung, and involvement of the left mid zone. An artificial pneumothorax was induced on the right side following haemoptysis, a good collapse was obtained, which was prevented from being complete by the presence of two adhesions over the upper and mid zones. An effusion developed later which was treated by aspiration and air-replacement, figure 13a is a dorsoventral film, taken after the completion of such a procedure, and the degree of collapse on the right side is well illustrated. In addition, a collection of fibrinous material, which is almost polypoid in type, may be seen at the base of the collapsed lung, the left lung shows a fairly diffuse infiltration of the mid zone.

Turning to the tomograms of the case, we find that in the ventral section (figure 13b) the degree of collapse is very good, neither adhesions nor collection of fibrin showing. The median section, figure 13c, (which incidentally reveals the left bronchus particularly well) still fails to show the presence of adhesions, but the faint shadow cast by the fibrinous collection may just be detected. Two centimetres deep to this, in the predorsal section (figure 13d), both the upper-lobe and mid-zone adhesions are clearly exposed, together with two partially compressed cavities in the middle and lower lobes, the mass of fibrin is also clearly seen. In the dorsal section (figure 13e), which is a further 2 cm behind the preceding level, there is a greater degree of collapse, but the adhesions are still faintly visible. Thus the lung is, as it were, billowed posteriorly, coming out to a certain extent in the median depths and being well collapsed again anteriorly, this effect being produced by the position of the adhesions, which are also situated medially.

A similar state of affairs has been revealed in other cases, and it would appear to be a not unusual finding in artificial pneumothorax for the collapse of the lung to be far from uniformly distributed, there may be an almost complete collapse over the anterior portion of lung, and yet the posterior zones may be unaffected, usually because of the presence of multiple small adhesions. When there are only one or two cord-like adhesions, they are more commonly found to be situated medially.

## 7 CONCLUSIONS

In this paper we have limited the description and discussion of results of tomographic investigation to cases of pulmonary tuberculosis, because, as yet, our experience of this adjunct to diagnosis in other conditions is

hardly wide enough either to warrant a description of the results or to enable us to come to any decision upon its value in such conditions. We have had under investigation cases of Hodgkin's disease, intrapulmonary cysts and lung abscess, but the field of cranial tomography has not been touched by us, and in the opinion of Chaoul this will be a particularly valuable field for investigation. There are also possibilities in the direction of tomography of the heart which remain to be explored, but, clearly, many modifications in technique will have to be elaborated before this particular organ can be demonstrated in recognizable sections. Nevertheless, despite the possibilities of tomography in a variety of conditions, it is our opinion that its greatest value at the moment lies in pulmonary tuberculosis, which manifests itself in such diverse ways that, even with every method at our command, the problem of diagnosis is at times very difficult.

While indicating its value, we have no desire to make exaggerated claims for tomography, and the indiscriminate use of the apparatus in all cases is certainly not called for. As we have made clear in a preceding section, tomographic investigation should only be used after routine radiological and screening examinations have been completed, it is then that problems calling for further elucidation may arise, and that tomography may be utilized as an additional aid. It is felt, however, that the cases described support the opinion that in tomography we have a valuable adjunct to the diagnosis and interpretation of pulmonary lesions, and an addition to the armamentarium of the physician and surgeon which one cannot afford to neglect.

## 8 SUMMARY

1 The sources of difficulty in the interpretation of a skiagram of the chest are discussed, and the need shown for some method whereby these difficulties may be overcome, either in part or in whole.

2 The method evolved—tomography—is described, and its advantages discussed.

3 The history of the development of the geometrical principles of tomography is described, and the difficulties of earlier workers in overcoming the practical problems of constructing a workable apparatus are discussed.

4 The present apparatus of Grossman and Chaoul is described, together with the technical points to be observed in the taking of tomograms.

5 A description of the tomogram of a normal lung is given, with a



résumé of the anatomy of the intrapulmonary structures, in order to establish a basis of comparison with films illustrating pathological lesions

6 Seven cases of pulmonary tuberculosis which have undergone tomographic examination are detailed, with special reference to (1) the analysis of gross disease, (2) the diagnosis of cavities, (3) the localization of cavities, (4) value of tomography in cases following thoracoplasty, and (5) the type of collapse in artificial pneumothorax

7 The possibilities of tomographic examination in other areas of the body, such as the skull and the heart, are mentioned, but it is clear that modifications in technique will be required before this new line of work can be fully explored While in no way supplanting the recognized methods of radiographic examination, it is felt that tomography, with its many advantages and refinements, cannot be ignored in the investigation of a case of pulmonary disease

We wish to express our thanks to Dr A Ross for his help in the investigation of these cases

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# EXPERIMENTAL TUBERCULOSIS INFECTION IN THE TADPOLE AND THE MECHANISM OF ITS SPREAD<sup>1,2</sup>

JOSÉ F. NONIDÉZ AND MORTON C. KAHN

In a previous communication (1) it was shown by us that tuberculosis could be successfully induced in the tadpole of the common leopard frog (*Rana pipiens*) after feeding the tadpoles a cold-blooded strain of tubercle bacillus, namely *Mycobacterium marinum*. The structure of the tubercles that developed was found not to differ in any essential point from those produced in mammals with human or bovine strains. *Mycobacterium marinum* was first isolated by Aronson (2) from an iguana which was found dead in the Philadelphia Zoological Gardens. A number of tubercles were noted in the lungs of the animal and also in the liver. When this *Mycobacterium* is injected intracutaneously in the guinea pig the neighboring lymph nodes become enlarged and succulent but go on to healing. Aronson also found that a small ulcer occurs at the site of inoculation. The organism is pathogenic for the chameleon and salamander and also for the frog. *Mycobacterium marinum* is acid- and alcohol-fast. Ziehl-Neelsen stained vertical sections of growing colonies made with a technique reported by us (3) reveal some non-acid-fast rods in addition. The organism grows luxuriantly at room temperature on Petroff's egg medium in from 3 to 5 days and elaborates an abundance of orange-colored pigment.

It appeared to us that the tadpole would possibly make a valuable experimental animal for the purpose of studying the mechanism of the dissemination of tubercle bacilli in various organs of the body after having been introduced *per os*, as the entire animal can be sectioned serially and all of the organs examined in the same creature at the same time. In the following sections we are reporting the results of experiments designed for this purpose.

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<sup>2</sup> This study is part of a group investigation being carried on in cooperation with the Medical Research Committee of the National Tuberculosis Association.

## MATERIAL AND TECHNIQUE

Young tadpoles of the leopard frog (*Rana pipiens*) were kept in sterile aquarium water contained in Stender dishes. A large loopful of a 5-day-old culture of *Mycobacterium marinum* was scraped from a slant of Petroff's egg medium and suspended in the water. After feeding on the bacteria the tadpoles were removed to other Stender dishes also containing sterile aquarium water.

Three experiments were carried out. In the first, the tadpoles were very young (5 to 7 days after hatching) and were allowed to feed on the bacteria for several days. They were soon overwhelmed without showing lesions of tuberculosis although numerous acid-fast organisms were found in the intestinal submucosa, the lungs and the liver. These tadpoles were fixed in alcohol or in a mixture of alcohol-chloral hydrate-formaldehyde, which gave better fixation.

In the second experiment, five young tadpoles were fed tubercle bacilli for one day, then they were given yolk from a hard-boiled egg during the four following days. On the fifth day they were fed tubercle bacilli again. One tadpole died during the night and could not be preserved for histological study. The other four were killed as follows: No. 1, killed 10 days after first, 5 days after second feeding; no. 2, killed 12 days after first, 7 days after second feeding; no. 3 and no. 4 killed 29 days after first, 24 days after second feeding. While only two feedings of bacteria were given it is possible that the tadpoles ingested bacilli from their own faeces, for the organisms seemingly multiply in the intestinal tract as they remain there for a long time after feeding has been discontinued. Study of the sections of the four tadpoles revealed the following conditions: No. 1, tubercle bacilli were present in the liver, first stages of formation of tubercles already seen. Also larger tubercles were in submucosa of intestine. No. 2, numerous tubercles were present in the liver, a few with beginning necrosis. No. 3, early and advanced tubercles with necrotic centers were present in liver. No. 4, mostly early tubercles, a few with beginning necrosis were found in the liver. A few tubercles containing bacilli were also seen in the spleen.

A third experiment was undertaken in order to trace the early stages of the infection. Six tadpoles were fed the *Mycobacterium* for one day. They were transferred to sterile water through five changes to avoid carrying over bacilli. They were killed 1 day, 2 days, 4 days, 5 days, 6 days and 7 days after feeding, respectively. Heidenhain's *Susa* fluid

was used for preservation, the fixed tadpoles being transferred directly to 95 per cent alcohol with a small amount of iodine. Although bacilli were already noticed in the mucous cells of the intestine as early as the second day after feeding, no reaction of the macrophages was observed until the sixth and seventh day.

In every case the tadpoles were dropped alive in the fixing fluid without making any cut in the skin. The tails were cut off after fixation and the whole body dehydrated, embedded in paraffin and cut into frontal serial sections (7-10 $\mu$  thick). The entire animal with the exception of the tail was thus included on the slides (figure 8). The sections were stained with hematoxylin-eosin for histological details, or with the Ziehl-Neelsen technique for the staining of the bacilli. The two techniques mentioned were used alternatively in the series of slides, and in this way it was possible to obtain sections of one and the same tubercle stained with the two methods used.

#### PASSAGE OF THE MYCOBACTERIUM THROUGH THE INTESTINAL WALL

The presence of large numbers of bacilli within the intestine does not lead to widespread lesions of the mucosa, nor do the bacilli appear in and among the epithelial cells in a way suggesting their active penetration into the mucosa. The passage of the bacilli through the intestinal barrier is a discrete process, taking place gradually and at separate points in a more or less accidental or passive manner since the *Mycobacterium* is a nonmotile organism. Before describing the processes involved, it will be convenient to review briefly the structure of the alimentary canal of the young tadpole.

The stomach is lined by a mucosa containing well-developed branched tubular glands. Two types of epithelium occur, namely, ciliated epithelium consisting of columnar cells and the secretory epithelium lining the glands. The latter extend from the ciliated epithelium into the loose submucosa and many come in close proximity with the muscular layer (figure 10). In the tadpole the submucosa is represented by a small amount of embryonic connective tissue, most of which lies between the gastric glands. Outside of this there is a muscularis consisting of an inner layer of circular smooth muscle fibres, and an outer, poorly defined layer containing muscle fibres of the same variety. Finally, external to the muscularis there is a serous coat represented by a thin layer of flattened cells, separated from the muscularis by a small amount of connective tissue.

The intestines of the tadpole have thin walls and are relatively much longer than in the frog. Two regions may be distinguished, the small and large intestine, respectively, which differ chiefly in the details of their epithelial cells and the relative abundance of the two cell-types occurring in the mucosa. The latter is not thrown into conspicuous folds, nor has it villi (figures 8 and 10). It consists of columnar cells and basal round cells, the latter being relatively few in number. The columnar cells are of two types: the numerous absorptive or chief cells which are ciliated, and the less numerous mucous or goblet cells. The nuclei of both types are elliptical. In Ziehl-Neelsen preparations the cilia of the chief cells stain light pink, and the cytoplasm may take a light lavender tone, while the mucous or goblet cells stain blue (figure 1). In the goblet cells two different aspects are noticed: in some cases they appear swollen since they are distended with mucous granules, while in others they appear much more slender as a result of the discharge of the mucus. Between the two conditions there are numerous intermediate stages.

Under the epithelium of the intestine there is a submucosa, the thickness of which varies according to the region, being thinnest in the large intestine. It contains connective tissue cells of a mesenchymatous type and numerous blood-vessels and lymphatics. Tissue phagocytes (macrophages or histiocytes) containing variable amounts of pigment granules occur scattered in this layer, but in the early part of the tadpole's life they are not numerous. Outside of the submucosa there are, as in the

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#### PLATE 1

Figures 1, 2, 5, 6 and 7 were drawn with a Zeiss apochromatic oil immersion 2 mm (numerical aperture 1.30) and compensating ocular 15, at a magnification of 1350 diameters. Figures 3 and 4, with the same objective and ocular 20 ( $\times 1800$ ). Ziehl-Neelsen technique.

Fig. 1 Chief (ciliated) cell of the intestine (centre) and two empty mucous cells showing intracellular bacilli.

Fig. 2 Phagocytosis of a degenerating mucous cell containing bacilli by a macrophage.

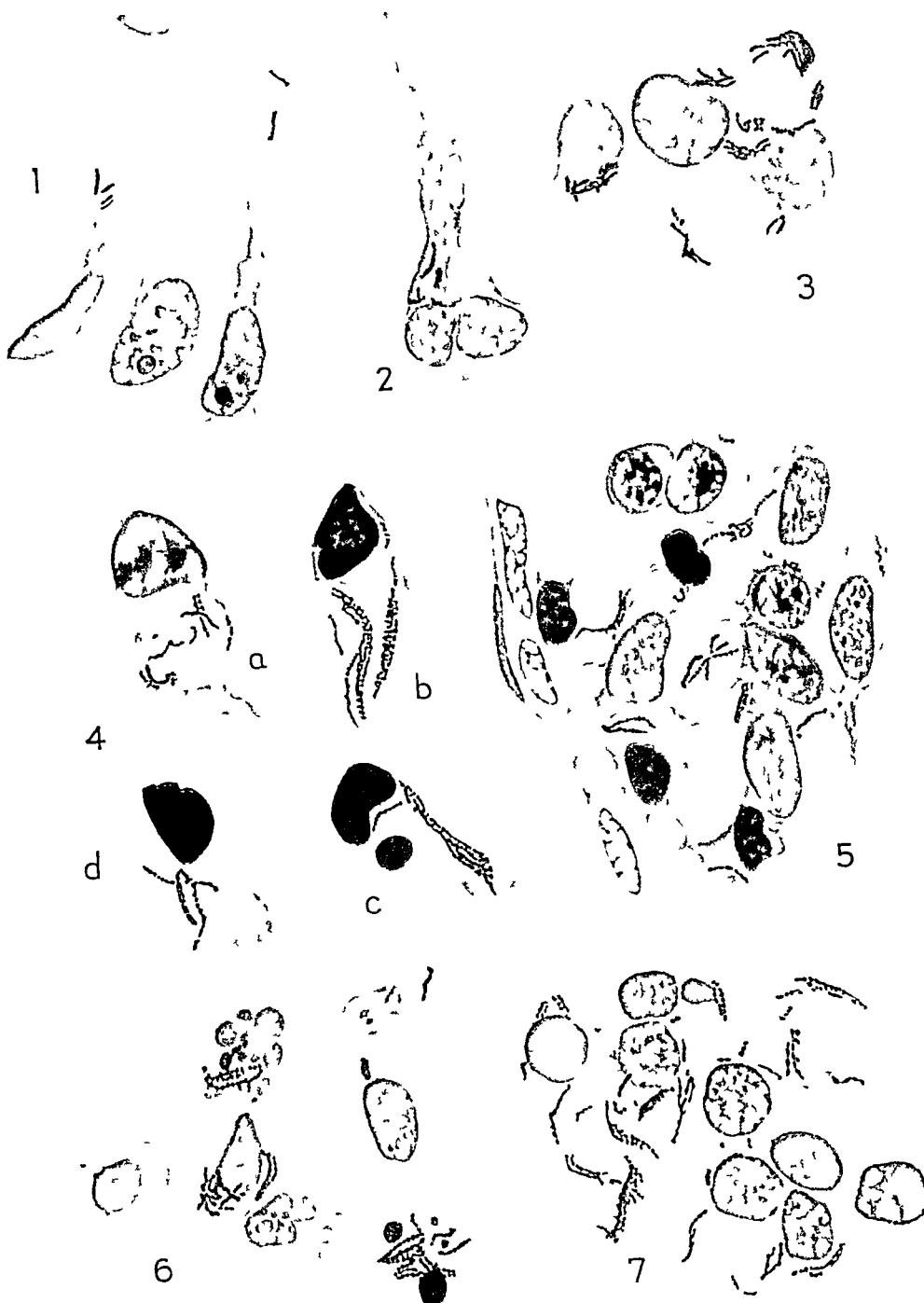
Fig. 3 Degenerating cells containing bacilli in the intestinal submucosa. A young macrophage seen.

Fig. 4 Four different stages of degeneration of macrophages with ingested bacilli from the periphery of a tubercle of the liver.

Fig. 5 Beginning of the formation of a tubercle in the submucosa of the small intestine. Young macrophages resembling lymphocytes and containing bacilli are seen in the figure. The cell elements with pink cytoplasm at the left of the figure are smooth muscle fibres.

Fig. 6 Diverse stages of degeneration of macrophages within the lung wall of a young tadpole still breathing through the gills.

Fig. 7 Free bacilli and nuclei of phagocytes in the lumen of one of the lungs of the same tadpole represented in figure 6.



stomach two muscle coats an inner circular and an outer longitudinal, the latter being covered externally by a thin serosa made up of much flattened mesothelial cells closely applied against the muscle fibres in view of the very thin subserous layer.

In the large intestine the epithelial cells of the mucosa are not so tall as in the small intestine, the mucous cells are much more abundant than in the latter. The cilia of the chief cells are quite long and apparently nonmotile, being cemented together by a substance produced through secretion or transformation of the cell membrane. No glands of any kind occur in the tadpole intestine.

A study of the different regions of the intestine of tadpoles which had been fed *Mycobacterium* for various lengths of time has shown that this organism never occurs within the chief cells but that it penetrates the empty mucous or goblet cells in variable numbers. Considering the very large numbers of bacilli in the intestinal lumen the scarcity of cells containing them is rather surprising. The most plausible explanation of the presence of the *Mycobacterium* within the cytoplasm of the mucous cells is that the organism enters passively soon after the mucus has been extruded from the cell, and that the penetration may be indirectly helped by the peristaltic contractions of the intestine. In the stomach intracellular bacilli were never found nor did they occur in the ducts of the gastric glands. The flow of gastric juice through the ducts may prevent their penetration.

The intracellular bacilli in the mucous cells (figure 1) appear within small, clear vacuoles. They are rather solid, short rods as compared with the bacilli within the macrophages and in the tubercles which show a more beaded aspect. While the presence of large numbers of *Mycobacterium* multiplying in the intestine does not affect the cells of the mucosa in a visible way the intracellular bacilli in the mucous cells exert a deleterious influence, causing degenerative changes and finally the death of the cell. At the beginning these degenerative changes are not easily distinguished from those changes undergone by a normal mucous cell after discharge of the mucus, but after some time their morbid nature cannot be doubted. The cell ceases to produce mucus and stains more deeply than the normal elements of its kind. The nucleus decreases in size, stains more deeply and shows a blurred aspect which may be followed by pyknosis. The cell as a whole shrinks and may lose its connection with the surface of the epithelium, moving passively toward the submucosa where eventually it will fall prey to the phagocytes.

From the preceding descriptions, it is evident that the main portal of infection is the mucous or goblet cell of the intestinal epithelium in the absence of degenerative changes of the mucosa induced mechanically or in some other way. The chief cells are protected by their well-developed brush border, and since they are closely placed and their peripheral portions are apparently cemented together by terminal bars, the penetration of the bacilli in the intercellular spaces is effectively prevented under normal conditions. Since the mucous cells occur everywhere in the intestine, it follows that there is no definite site for the beginning of the infection.

The fate of the mucous cells containing the *Mycobacterium* seems to be the same in all cases, that is, they are phagocytized by macrophages occurring in the area, the phagocytosis taking place during different phases of their degeneration.

#### PHAGOCYTOSIS OF THE BACILLI BY MACROPHAGES

The origin and behavior of the tissue phagocytes or macrophages is well known through the exhaustive studies of E. R. Clark and E. L. Clark (4) on the tail of the living tadpole. According to these investigators, the amphibian macrophage is homologous with the mammalian macrophage, also known as histiocyte, clasmatocyte, polyblast and reticuloendothelial cell, to mention a few names. In the present article, the term macrophage will be used since it is descriptive of the main activity of this important cell-type without implying a definite origin.

The macrophages of the tadpole develop quite early and are not always derived from the blood-stream, since they may arise from the mesenchyme at a stage in which no leucocytes occur in the blood. They are the only wandering cells which take the neutral red stain to any noticeable degree. They also take up carmine, India ink and pigment granules, and engulf erythrocytes, all types of degenerating cells and extraneous substances injected in the tail such as cream, yolk of egg, starch, agar, gelatine, gum arabic and even diluted croton oil which produces an aseptic inflammation of the tissues of the tail (Clark and Clark (5) (6) (7)). After phagocytosis the cells under consideration usually develop pigment granules in their cytoplasm. In the living tadpole they often penetrate the lymphatics and blood capillaries, which they may leave after some time in the absence of any material to phagocytize. They also ingest cells before they have actually degenerated. "When a cell begins to die, the macrophages of the neighborhood make a 'bee-line'



for it. If a single macrophage reaches the dead cell, or its remnants, it proceeds to ingest them. Frequently two or three macrophages reach the dead cell simultaneously, whereupon a struggle occurs over it or its remains" (Clark and Clark (5) p. 115). Sometimes phagocytosis occurs before the various stages of degeneration of the cell have taken place. When no macrophages occur in the neighborhood, the cell may degenerate and break up and its remnants be taken up by macrophages arriving from other areas. After phagocytosis of a large mass of debris and dead cells the macrophages become sluggish and even temporarily sessile.

As to the origin of the macrophages in the tadpole tail in later stages of the larval life, the Clarks have demonstrated by actual experiments that they may also arise from large mononuclear leucocytes of the blood. In the words of these authors "the monocytes of the blood are identical with the clear mononuclear phagocytes of the tissue, and they are both capable of enlarging to form typical tissue macrophages. The large pigmented macrophage is, therefore, a monocyte which has emigrated from the blood vessel and has been carrying on phagocytosis" ((6) p. 179).

In the fixed tadpole, stained with hematoxylin-eosin or the Ziehl-Neelsen technique, the macrophages that have been engaged in phagocytosis appear as rather large cells with clear cytoplasm containing variable amounts of pigment granules, and a large, clear nucleus the shape of which is also variable. In the intestine they occur in the submucosa, and two or three of these cells may appear clustered together. It is not unusual to find bacilli in their cytoplasm, more or less masked by the pigment therein. As already stated, in very young tadpoles the macrophages are scarce. In the older larvae not only are they more abundant but many of them appear in the early stages of their development, during which they closely resemble the large mononuclears of the blood since they do not contain pigment and have a more deeply stained, basophilic cytoplasm. Such young macrophages may attack degenerating cells, and in areas of formation of tubercles they may show ingested bacilli (figure 5).

In the course of our investigations, we have been able to detect numerous cases of phagocytosis of mucous cells containing the *Mycobacterium* by the macrophages. In agreement with the observations of the Clarks on the tail of the living tadpole the macrophages may attack and engulf mucous cells before they have degenerated, one case of this sort has been represented in figure 2. The macrophage in this figure is seen engulfing

the basal portion of a mucous cell which has already lost contact with the surface of the mucosa, and, therefore, does not appear as tall as the more normal mucous cells of figure 1. In other instances, the macrophages attack mucous cells in which the disintegration of the nucleus and cytoplasm is much more advanced. Two or more macrophages may sometimes participate in the process, and if one or more of them should die they may in turn be engulfed by other macrophages of the submucosa (figure 3).

Although the Clarks have never been able to see the degeneration of the macrophage and regard this cell as the hardest of all cell-types found in the tail of the living tadpole, in tadpoles infected with the *Mycobacterium* there are abundant examples of death of macrophages which have engulfed bacilli, either directly or through phagocytosis of cells containing them. Unquestionably the same deleterious effect exerted by the *Mycobacterium* on the mucous cells is exerted on the macrophages, and their death in large numbers contributes in no small measure to the formation of the necrotic area of the tubercles. It seems as though the macrophages, although able to digest cells and their debris, and some extraneous substances such as cream, yolk of egg, etc., are not able to kill the bacilli, at least in those cases in which the latter occur in fairly large numbers within the cell.

An example of degenerative phases of macrophages with engulfed bacilli is shown in figure 4, copied from the periphery of a fairly large liver tubercle. Cell *A* shows nuclear changes manifested in clumping of the chromatin granules and partial dissolution of the cytoplasm, in *B* the cell, containing a large number of bacilli, shows a clearly pyknotic nucleus, which in cell *C* has broken in two unequal parts. Finally, cell *D* shows dissolution of the cytoplasm with impending liberation of the bacilli. Similar stages are seen in figure 6, copied from the lung of a much younger tadpole, dead after 7 days of continuous feeding with *Mycobacterium*. The degeneration of the phagocytes is, therefore, a widespread and constant process, leading to the liberation of the ingested bacilli in the tissue in which the macrophage happens to be at the time.

Although macrophages may be killed by the bacilli which they have ingested, they do not always degenerate *in situ*, but they are able to move about and wander for some distance, a fact that would indicate that the degeneration of these cells is a slow process. Thus they are able to spread the infection. Since, as shown by the Clarks, the macrophages are able to cross the endothelium of the blood vessels and lymphatics

the vascular route of the infection deserved to be investigated carefully. We have, therefore, paid considerable attention to this aspect of the problem, to be considered in the following section.

#### MIGRATION OF THE MACROPHAGES WITH INGESTED BACILLI

In tracing the migrations of the macrophages with ingested bacilli we wish to emphasize the fact that the tadpoles were dropped alive in the fixing fluid, and that no cuts of any kind causing haemorrhage or spilling of the body fluids were ever made. In this regard our material differs from any material obtained from adult animals and humans. Furthermore, in our case it was possible to study *a whole tadpole in serial sections and investigate not only all the organs present during larval life but also the larger vessels and the cavities of the heart with the blood contained therein*. Under these conditions the only displacements of the cells and organs were those incidental to shrinkage during the process of dehydration and embedding.

After a study of hundreds of sections passing through the heart, the venae cavae, the portal system of the liver and the portal-renal system present in the tadpole we can conclude that macrophages containing ingested *Mycobacterium* do not occur in the blood-stream. This peculiar behavior is difficult to explain inasmuch as there is direct evidence of the passage of the macrophages into the blood capillaries (Clark and Clark). As to free bacilli and bacilli included within cell debris in the blood our observations are also negative. While in the latter stages of the tadpole life all the cell elements of the adult are present in the blood and the polymorphonuclear leucocytes can be distinguished from other leucocytes, repeated observations have failed to demonstrate the presence of intravascular leucocytes containing *Mycobacterium*.

In the serosa of the intestine, which, as already stated, is rich in capillaries, macrophages with ingested bacilli are occasionally seen within the vessels. It is difficult, however, to decide whether the phagocytic elements occur within a blood capillary or a lymphatic. We would hesitate to state, therefore, that macrophages containing bacilli do not penetrate the blood vessels, but we can say that they were never seen in vessels containing erythrocytes.

When we take into account that typical tubercles develop in the liver and occasionally also in the spleen, and that they are not seen in other organs—the intestine excepted—the most plausible explanation is that the macrophages containing bacilli reach these organs via the lymphatics, and that they are arrested there by the fixed reticuloendothelial elements.

(Kupffer cells of the liver, splenocytes) It might be possible, however, that the migrating macrophages enter these organs directly after leaving the intestinal wall by crossing the thin muscularis and the serosa. In the case of the liver such penetration does not seem likely, for the youngest tubercles are to be found in the portal of this organ among the hepatic ducts.

#### LUNGS

Of particular interest is the presence of large numbers of *Mycobacterium* in the walls of the lungs and within the cavity of these organs. In the tadpole the lungs are simple sacs with thin walls, extending from the ventral aspect of the pharynx on either side of the midline. Since there is no diaphragm they lie in the abdominal cavity in contact with the organs enclosed therein, including the intestine. It is possible then, for macrophages leaving the intestine to work their way among the flattened cells of the serosa of the lungs—representing the visceral pleura of the mammal—and after crossing the lung tissue, fall into the lung cavity. During the early stages of life the tadpole breathes through gills, the lungs are still developing and appear as sacs which do not communicate with the outside since the region representing the larynx has not attained full development and lacks a lumen. Later on the folds of the glottis, fused together up to this moment, separate and a communication between the lungs and the pharynx is thus established, the tadpole begins to use the lungs, swimming to the surface of the water to obtain air.

The presence of large numbers of *Mycobacterium* in the lungs of young tadpoles which are still breathing through their gills shows conclusively that the bacilli had not been inhaled, but that they had been "dumped" into the lung cavity by migrating macrophages the nuclei of which appear among the bacilli (figure 7). Migration of the macrophages into the lungs does not cease after these organs have started functioning, for they are seen within the lung wall which appears still thinner since the lungs are now distended with air. However, collections of bacilli and degenerating macrophages are not seen in the lung cavity because they are promptly removed through the action of the cilia of low columnar epithelial cells which represent the bronchial epithelium of the mammal. Even though the older tadpoles breath through the lungs the penetration of bacilli from the pharynx into these organs is highly improbable since the necessary mechanisms to prevent the passage of food into the respiratory system are already operative.

Contrary to our suppositions the presence of large numbers of *Myco-*

bacterium in the walls of the lungs does not lead to the formation of tubercles in these organs. There is no question that macrophages degenerate within the lung tissues (figure 6) and that numbers of bacilli are thus released, but they are apparently phagocytized by young macrophages which migrate into the lung cavity after crossing the flat epithelium forming the inner lining of the rudimentary alveoli. The latter are shallow outpocketings of the lung wall, which, in addition to the ciliated cells, contains numerous smooth muscle fibres. Neither muscle fibres nor ciliated cells occur in the alveoli. Removal of desquamated cells, macrophages and bacilli through ciliary action may be relatively easier in the tadpole than in the mammalian lung since there are no long alveolar and bronchial passages. In this respect, the lung of the tadpole is an important means for the elimination of *Mycobacterium*. Whether lung tubercles arise in the frog, in which the lungs have thicker walls and a somewhat more complex structure, is a point which requires investigation.

#### FORMATION AND STRUCTURE OF THE TUBERCLES

In the interpretation of the lesions produced by the *Mycobacterium marinum* in the organs of the tadpole, it must be remembered that we are dealing with a larva, that is, a stage of development which is intermediate between the embryo and the adult. Under such conditions it would be logical to expect certain differences in the formation and structure of the tubercles, yet the reaction of the tissues of the tadpole to the infecting agent is remarkably similar to that of the mammalian tissues. As is the case in the latter, the slight differences to be observed in the tubercles are due less to variations in the character of the inflammatory reaction than to differences in the structure of the organs in which the lesions

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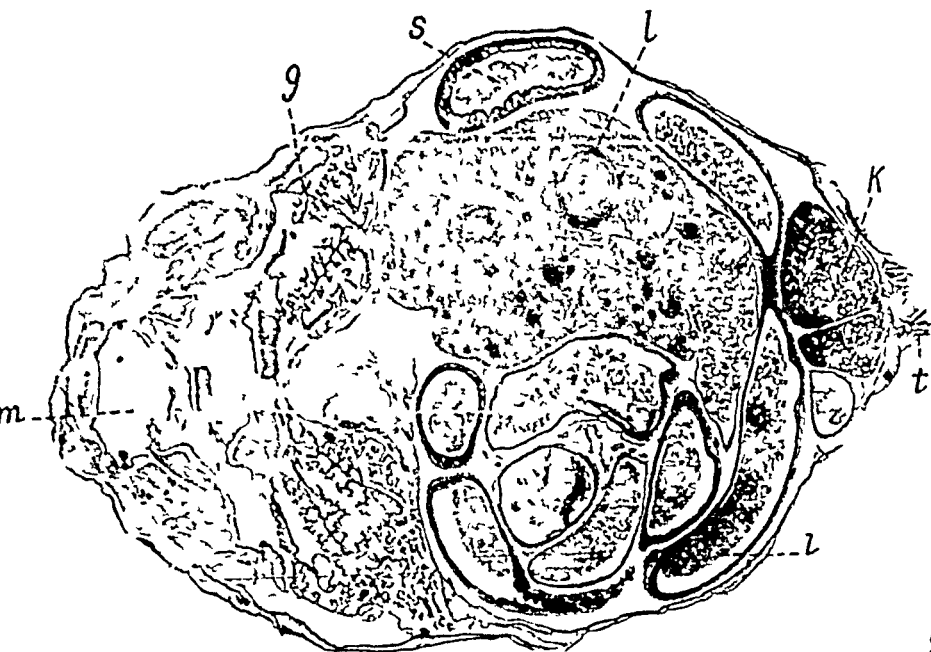
#### PLATE 2

All figures in this plate are unretouched photomicrographs of sections stained with hematoxylin and eosin.

Fig 8 Frontal section of the entire tadpole showing organs of the abdominal cavity. Numerous tubercles of various sizes are seen in the liver, l, g, gills, i, intestine, k, kidney (mesonephros), l, liver, m, buccal cavity, s, stomach, t, root of the tail.

Fig 9 Small tubercle in the submucosa of the intestine. Notice normal aspect of the mucosa. The submucosa appears thicker than in the normal areas at the level of the tubercle.

Fig 10 Small tubercle in the pyloric region of the stomach. Some of the epithelial cells of the mucosa are undergoing degeneration, as well as the cells lining the glands next to the tubercle. The group of cells with clear cytoplasm in the mucosa at the right of the tubercle belong to the duct of a gland.



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develop. The formation of tubercles in the diverse organs in which they have been observed will be considered in the following paragraphs.

*Intestine* Since the intestine is the portal of infection in tadpoles fed the *Mycobacterium* numerous tubercular lesions are to be found in this part of the digestive tract. In their earliest stages they consist of small accumulations of cells around bacilli presumably released by degenerating mucous cells and macrophages. In slightly later stages the number of cells has increased, and the conglomerate has become spherical. In every case the tubercles begin to develop in the submucosa, the mucosa in most cases does not seem disturbed or only to a slight degree.

Figure 5 shows a small accumulation of cells in the submucosa. The cell conglomerate consists of fibroblasts and roundish cells with a large nucleus and basophilic cytoplasm somewhat resembling lymphocytes. These round cells (m), some of which contain bacilli, we interpret as young mononuclear leucocytes (monocytes) migrated from the vessels. As already stated, in the tadpole this cell-type develops into the macrophage or histiocyte which wanders in the tissues. Bacilli also occur in the cytoplasm of the fibroblasts, but their presence in these cells may not be due to phagocytosis since in the living tadpole the connective tissue cells may withdraw some of their processes and form new ones, which may enclose the bacilli. A few cells with pyknotic nuclei, presumably fibroblasts, also occur in the area copied.

A larger tubercle from the submucosa of the intestine is illustrated in figure 9. The necrotic centre characteristic of the larger tubercles has not yet appeared in this case. The round deeply-stained nuclei we interpret as belonging to young monocytes which have migrated from the vessels.

As the growth of the tubercle proceeds a number of cells occupying its centre degenerate. In sections stained with the Ziehl-Neelsen technique the cell debris in the centre of the tubercle stains light pink or

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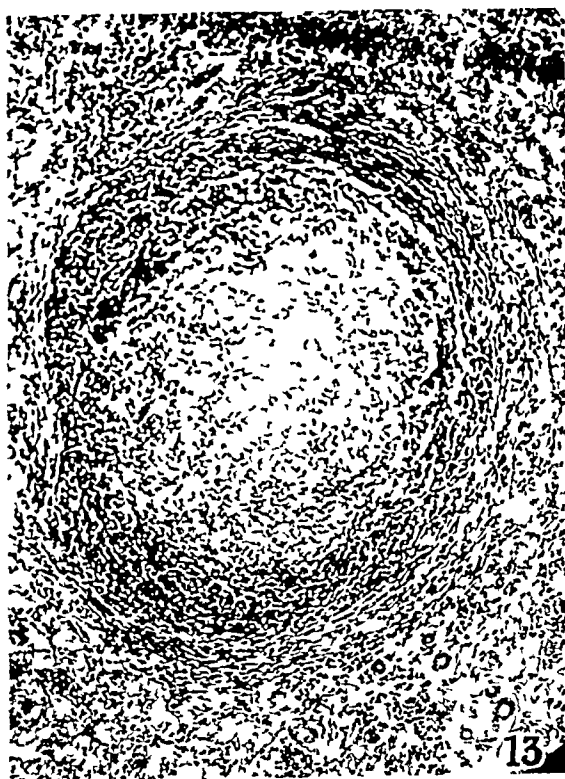
#### PLATE 3

All figures in this plate are unretouched photomicrographs of sections stained with hematoxylin and eosin.

Fig. 11. Large tubercle with necrotic centre developed in the submucosa of the intestine. The latter appears filled with food, masses of pigment and clumps of bacilli. The area of attachment of the tubercle to the submucosa is clearly seen at the right of the tubercle.

Fig. 12. Small tubercles in the portal of the liver. Sections of the hepatic ducts and branches of the portal vein seen in the figure.

Fig. 13. Large tubercle with necrotic centre, liver. The tubercle photographed is the largest of figure 8.





pale lavender, and numerous bacilli are found in this area. Pyknotic nuclei and nuclear fragments also abound. Around the necrotic centre we find a fairly dense area consisting of elongated nuclei and numerous roundish cells. Some of the latter are macrophages resembling the epithelioid cells of the mammalian tubercle. They appear in different stages of degeneration and often contain bacilli. The elongated nuclei, also showing diverse stages of degeneration, belong to fibroblasts. As in the case of the mammalian tubercle there is apparently fibroblastic proliferation, though few or no mitoses were observed in support of this interpretation. In large tubercles the fibroblasts are arranged concentrically, and they form the outer layer of the tubercle (figure 11). As compared with the mammalian tubercle the corresponding structures of the tadpole show a more marked degree of fibroblastic hyperplasia, which may perhaps be explained on the assumption that the proliferative capacity of the fibroblasts is greater since they are still embryonic cells. The characteristic giant cells, usually but not always present in the mammalian tubercle, are absent in the tubercles of the tadpole, regardless of their location. Eosinophilic and neutrophilic leucocytes occur around the tubercles but as far as we have been able to see they do not contain bacilli.

Diverse stages of the formation of tubercles were also found in the mesentery. As in the case of the intestine the fibroblasts are also numerous around the tubercle. Numerous young macrophages are seen scattered among the connective tissue elements of the mesentery, suggesting that they may arise extravascularly in areas comparable with the milky spots of the mammalian mesentery.

*Stomach.* Tubercles in the stomach must be of rare occurrence since only one was observed in the tadpoles studied, it occurred in the submucosa of the pyloric region (figure 10). Its histological structure is similar to that of the tubercles of the intestine, but since the glands of the stomach extend through the submucosa and reach the inner muscle coat, the growing tubercle has displaced the glandular elements, some of which appear undergoing degeneration. As in the case of the intestine the rest of the mucosa appears intact with the exception of a few degenerating ciliated cells, clearly seen in the figure. Since bacilli were never found within the gastric glands it does not seem likely that the infection started in the stomach. In all probability the bacilli reached the organ from some other area.

*Liver.* The largest tubercles were found in the liver in which they can

be seen in sections with the naked eye (figure 8). Furthermore, the tubercles in the liver are more numerous than in any other organ and their size ranges from small, spherical accumulations of cells to large tubercles with conspicuous necrotic centres (figures 8 and 13). The smaller or younger tubercles are found near the portal of the liver among the hepatic ducts and larger branches of the portal vein (figure 12).

In tadpoles raised in the laboratory on a diet of yolk of hard-boiled egg the liver cells are infiltrated with fat. The fat drops are of uneven size and do not merge to form a large drop, accordingly the nucleus remains in the centre of the cell or is slightly eccentric, and the pressure exerted by the fat stored in the cytoplasm on the nuclear wall changes the outline of the nucleus, which usually has a somewhat crenated aspect. The smallest tubercles in the liver are very similar to the intestinal tubercles, and they lack necrotic centres (figure 12). The latter begin to appear in medium-sized tubercles, attaining greater development than in the intestine. The reaction of the tissues to the *Mycobacterium* is relatively more marked in the liver than in the other organs, but this may be partly due to the presence of large numbers of reticuloendothelial cells in the liver. These cells move in large numbers toward the incipient tubercle and in so doing they may occlude the sinusoids, thus cutting off the blood supply to the liver cells which degenerate rapidly. Since the latter are loaded with fat drops they release the fat. The clear aspect of the necrotic centre in slides stained with the routine methods may be due to the presence of the liberated fat. Large numbers of bacilli occur within the centre as well as fragments of nuclei, some belonging to the degenerated macrophages, others to the dead liver cells. With further growth the tubercle compresses and kills the liver cells in the immediate vicinity. Around the necrotic centre there is a dense area formed by proliferated fibroblasts and numerous macrophages and monocytes, both healthy and undergoing degeneration. In some cases they contain numerous bacilli, which are released upon disintegration of the cell (figure 4). Outside the tubercle there is a layer of proliferated fibroblasts arranged concentrically, as in the intestine.

*Spleen.* Tubercles in the spleen were found only in one tadpole. The tubercles in these cases were small and lacked necrotic centres. They resembled closely the corresponding structures of the intestine. Bacilli in the spleen were observed time and again in the several tadpoles, but since tubercles are rare in this organ it is quite possible that the bacilli may be destroyed there if present in moderate numbers.

## COMMENT

Any attempt to extend the results of the present study to the higher vertebrates and particularly to the mammals would seem unwarranted in view of the fact that the tadpole is the larva of a cold-blooded animal. Yet the study of tuberculosis induced by feeding in this form discloses certain features which deserve emphasis because they have been the subject of controversy in the field of mammalian tuberculosis.

Our investigations demonstrate beyond reasonable doubt that typical tuberculosis arises after ingestion of the bacilli and under conditions which preclude the penetration of the organism via the respiratory system. They also disclose that the intestinal barrier can be surmounted—in the absence of previous pathological changes—by a nonmotile microorganism, and that access to the mucosa is furnished by the normal process of discharge of the mucus by the goblet cells. The penetration of the bacilli in the empty goblet cells seems to be accidental, if we judge from the relatively small proportion of the cells containing them. Once the intestinal barrier has been surmounted the cell elements that constitute the defenses of the body are unable to cope with the infecting agent, for, although they phagocytize it and the cells in which it is contained, they are not successful in checking its spread. In fact, the macrophages which carry bacilli in their wanderings through the tissues and lymphatics become the most important agents in the spread of the disease. Considering the large numbers of bacilli in the tubercles it is evident that they grow and multiply within the latter, it is also quite possible that they reproduce within the infected mucous cells and perhaps also while in the cytoplasm of the macrophages. That the latter can kill the bacilli if present in small numbers is quite likely, but if too many of them have been phagocytized the reverse may happen, that is, the bacilli may slowly cause the death of the macrophage. (In this connection, however, the work of Sabin and Doan (8) should be cited. According to these observers the mononuclear phagocytic cells may be divided into two strains. The clasmatocytes phagocytize tubercle bacilli freely and fragment them, while the monocytes stimulated to metamorphose into the typical epithelioid and giant cells of the Langhans type retain the tubercle bacilli intact with power to survive and multiply over a considerable period of time. These observations were made on rabbits with bovine tubercle bacilli as the infecting agent.)

In very young tadpoles continuously fed the bacillus the infection is

fatal within a few days. In older tadpoles in which the leucocytes are already present in the blood the infection can be fought more successfully. Numbers of mononuclear leucocytes leave the blood-stream to enter the affected tissues. They closely resemble lymphocytes but are phagocytic whereas the latter, as shown by the Clarks in the living tadpole, lack the power of phagocytosis. We regard the phagocytic cells of the tissue as young monocytes. Their similarity with the lymphocytes is so striking that in the frog they have been regarded as arising from lymphocytes (Jordan (9) (10) ). For our purpose further discussion of this point is unnecessary since we are concerned only with the type of blood cell which is capable of phagocytosis after leaving the blood-stream, not with its origin in the haemopoietic centres of the tadpole, located in the kidneys (mesonephroi) and, according to Jordan and Spedel (11), to some extent also in the spleen.

While numbers of monocytes leave the blood-stream and phagocytize bacilli and dead cells, thus becoming macrophages, they do not return to the blood-vessels after once engulfing the bacilli. This important point could be settled in the tadpole because the whole animal had been sectioned serially, and no cut leading to haemorrhage was made prior to fixation. If macrophages containing bacilli enter the intestinal capillaries one would expect to find them in the larger vessels and the cavities of the heart. Our search for such cells in the blood-stream has always led to negative results. We are forced to conclude, therefore, that the route followed by the macrophages containing bacilli must be a different one, either through the lymphatics or by way of the body cavity or both. We are aware that the early presence of tubercles in the liver would suggest the arrival of the bacilli to this organ through the portal vein, but we have never been able to see cells containing them in this vessel or in its main branches within the liver. On the other hand, it must be remembered that the tadpole lacks lymph nodes and that macrophages with bacilli within the lymphatics would not find any obstacle interposed in their path.

Finally, a point that deserves comment is the presence of large numbers of bacilli in the lungs at a time in which these organs have not started functioning and have no open communication with the pharynx. Along with the bacilli there occur numbers of nuclei belonging to the degenerating macrophages that transported them into the lung cavity. We have already indicated that the passage of macrophages from the intestine to the lung wall is anatomically possible since the tadpole lacks a dia-

phragm, but, since the lung has an efficient mechanism for the elimination of particulate foreign matter, we may ask ourselves whether this "dumping" of the bacilli is merely accidental or whether it constitutes an important route for the elimination of the pathogenic agent. In the functioning lung bacilli and macrophages are still seen in the lung wall, but very few or none occur in the cavity of this organ since they may have been eliminated through the activity of the numerous ciliated cells.

#### SUMMARY AND CONCLUSIONS

1 Tadpoles fed *Mycobacterium marinum* develop typical tuberculosis. The portal of the infection is represented by the goblet cells of the intestine after discharge of their mucus, the bacilli entering them in a more or less accidental manner. The goblet cells with enclosed bacilli undergo degeneration and are engulfed by tissue phagocytes (macrophages).

2 The macrophages with ingested bacilli wander about the submucosa of the intestine and may enter the lymphatics or pass into the body cavity. They slowly degenerate and their remnants are taken up by other macrophages which further spread the infection since they are apparently unable to kill the bacilli. Many macrophages arise from mononuclear leucocytes (monocytes) migrated from the blood-vessels or, as previously shown by the Clarks, in the tail of the living tadpole.

3 The absence of macrophages with ingested bacilli in the blood-vessels and heart, repeatedly verified through a study of serial sections of entire tadpoles, shows that the infection does not spread through the blood. The lymphatics and the body cavity are the main routes followed by the macrophages carrying the bacilli.

4 Numerous macrophages leave the intestine and enter the lung wall where they may degenerate and release the bacilli, which are taken up by other macrophages and "dumped" into the lung cavity. In young tadpoles in which the lungs are not yet functioning large numbers of bacilli and degenerated macrophages occur within the cavity of the lung. In older tadpoles with functional lungs, bacilli appear within the wall of these organs but both the macrophages and bacilli reaching the cavity are apparently eliminated through the action of the ciliated cells of the inner lining of the lung cavity.

5 Tubercles in various organs are described. Large tubercles contain distinct necrotic centres in which bacilli and fragments of degenerated nuclei abound. Around the necrotic centre there is a dense area occupied

by macrophages resembling the epithelioid cells of the mammalian tubercle, and proliferated fibroblasts. The latter are more abundant than in the mammal. Giant cells were never observed in any of the tubercles examined.

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# COEXISTENCE OF LYMPHOCYTIC LEUKAEMIA AND FAR-ADVANCED PULMONARY TUBERCULOSIS<sup>1</sup>

Report of a Case

W J RYAN AND E M MEDLAR

The coexistence of infectious diseases of serious import and of leukaemic processes has led to a belief that leukaemia may be fundamentally dependent upon bacterial infection, that is, aetiologically leukaemia might be of an infectious nature. Bacterial agents of different kinds have been reported in connection with blood dyscrasias but more attention has been attracted to the tubercle bacillus as the aetiological agent for these dyscrasias than any other single type of bacteria. Reports on the association of the tuberculous infection with Hodgkin's disease and with myelogenous leukaemia are much more numerous than with lymphocytic leukaemia. Ryan (1) reported a case without necropsy of moderately advanced pulmonary tuberculosis which developed an acute lymphocytic leukaemia and died in a few weeks. Weil, *et al* (2) reported a case with tuberculous cervical lymph nodes but without pulmonary involvement. Feigenbaum's case (3) had generalized miliary tuberculosis with but slight pulmonary involvement and it is doubtful if this case was one of lymphocytic leukaemia. Fischer's case (4) was one of chronic lymphocytic leukaemia and generalized miliary tuberculosis which developed subsequent to the onset of the leukaemic process. Parker, *et al* (5) found evidence of tuberculosis in three out of thirty cases of lymphocytic leukaemia and in all three of these cases the tuberculosis was healed.

The case we report is of especial interest in that he had a clinically active far-advanced pulmonary tuberculosis with cavitation, he was under sanatorium treatment for over six months so that he could be carefully studied, he had a blood-picture typical of chronic lymphocytic leukaemia, and necropsy was performed.

<sup>1</sup> From the Summit Park Sanatorium, Pomona, New York, and the Hegeman Memorial Research Laboratory of the Metropolitan Life Insurance Company Sanatorium Mount McGregor, New York.

*Case Report*

O A, German-American, married, age 55 years, was admitted to the Summit Park Sanatorium on June 4, 1935, with the diagnosis of far-advanced pulmonary tuberculosis. Father died of pulmonary tuberculosis at the age of 31, and his wife succumbed to the same disease in 1931. The patient gave a

TABLE 1  
*Blood findings during sanatorium residence*

DATE	ERYTHROCYTES		LEUCOCYTES						
	Total in millions	Hemoglobin	Total in thousands	Neutrophils	Immature neutrophils (100 counted)	Lymphocytes	Monocytes	Eosinophils	Basophils
	grams			per cent	per cent	per cent	per cent	per cent	per cent
6/12/35	2.18	6.6	280	2 (5,600)	—	98	—	—	—
6/18/35	3.34	—	331	2 (6,600)	—	98	—	—	—
6/26/35	2.98	6.46	364	2 (7,300)	52 (3,800)	98	—	—	—
7/ 3/35	3.34	4.95	338	2 (6,800)	68 (4,600)	97	0.5 (1,700)	—	0.5
7/11/35	2.62	—	340	2 (6,800)	64 (4,300)	98	—	—	—
7/18/35	2.27	5.50	250	1.5 (4,000)	74 (2,900)	98	0.5 (1,200)	—	—
7/25/35	2.88	—	302	2 (6,000)	50 (3,000)	97	1 (3,000)	—	—
8/ 1/35	3.30	6.32	287	3 (8,600)	50 (4,300)	96	1 (2,800)	—	—
8/ 8/35	3.10	6.18	295	2 (5,900)	67 (3,900)	97	1 (2,900)	—	—
8/15/35	2.64	6.05	271	2 (5,400)	75 (4,000)	97	1 (2,700)	—	—
8/23/35	—	5.91	250	2 (5,000)	75 (3,700)	98	—	—	—
8/29/35	—	—	290	2 (5,800)	65 (3,800)	98	—	—	—
9/ 4/35	2.00	5.50	260	3.5 (9,300)	68 (6,300)	96	0.5 (1,300)	—	—
9/12/35	—	—	240	3 (7,200)	67 (4,800)	97	—	—	—
9/19/35	2.61	5.50	227	4 (9,100)	63 (5,700)	96	—	—	—
9/27/35	3.50	5.50	263	4 (10,500)	50 (5,200)	96	—	—	—
10/ 4/35	3.12	5.50	220	2 (4,400)	50 (2,200)	98	—	—	—
10/11/35	3.30	5.50	230	3 (6,900)	65 (4,500)	96	1 (2,300)	—	—
10/19/35	3.25	5.50	250	5 (12,500)	60 (7,500)	94	1 (2,500)	—	—
10/26/35	3.32	5.50	200	3 (6,000)	67 (4,000)	96	1 (2,000)	—	—
10/30/35	3.16	5.50	180	3 (5,400)	72 (3,900)	96	1 (1,800)	—	—
11/ 9/35	3.39	5.37	192	5 (9,600)	70 (6,700)	93	1.5 (2,700)	0.5	—
11/19/35	2.98	5.23	154	4 (6,200)	72 (4,500)	95	1 (1,500)	—	—
12/ 3/35	2.78	4.81	212	3 (6,400)	90 (5,800)	96	1 (2,100)	—	—
12/14/35	3.10	4.81	160	2 (3,200)	94 (3,000)	97	1 (1,600)	—	—

history of cough since 1929 and was suspected of being tuberculous, but no chest examination at the clinic was permitted until a few days before his admission. Physical examination revealed a very ill, emaciated, anaemic appearing patient. There was extensive disease throughout the entire left lung with a large cavity in the upper lobe. The right lung revealed physical signs in the



upper one-third Palpation of the abdomen revealed a markedly enlarged spleen which extended to the midline and downward to the crest of the ilium No demonstrable change in the size of the spleen was found subsequent to his admission No palpable lymph nodes were found Physical examination was otherwise essentially negative X-ray of the chest demonstrated a very dense right hilum shadow with considerable soft nodular infiltrate throughout the lung There was a large area of rarefaction in the left upper indicating probable cavity formation During the patient's residence sputum was fairly copious and was persistently positive for tubercle bacilli (Gaffky V to VIII) The unusual *blood picture* (figure 5) found on the routine examination after the admission of the patient led us to a careful weekly study of the circulating blood The results obtained are given in table 1

The patient was strictly confined to bed from the date of his admission Temporary improvement in his temperature and pulse rate took place during the first two months, but about the middle of August, 1935, two months after his admission, his temperature again rose and persisted at from 101° to 103°F with a pulse rate of 110 to 130 The patient died on December 16, 1935

### *Necropsy<sup>2</sup>*

The essential gross findings were Extensive tuberculosis of left lung, with a large cavity in the upper lobe and smaller cavities in the lower lobe, numerous small tuberculous foci in the right lung, enlarged peribronchial lymph nodes which on section did not appear tuberculous, pericardial effusion, obliterative pleuritis (bilateral), enlarged mesenteric lymph nodes, abundant reddish bone-marrow, enlarged spleen (9 x 6 x 4 inches) which did not appear to be tuberculous

Microscopical examination of the lung tissue showed The wall of the cavity was composed of fibrous tissue with marked lymphocytic infiltration in the outer portion (figure 4) and neutrophilic infiltration (figure 3) in the inner portion, tubercle bacilli were easily demonstrable in the inner surface of the cavities, in other portions of the lung there were caseous foci, typical tubercles with monocytes, giant cells and some lymphocytic infiltration, and considerable

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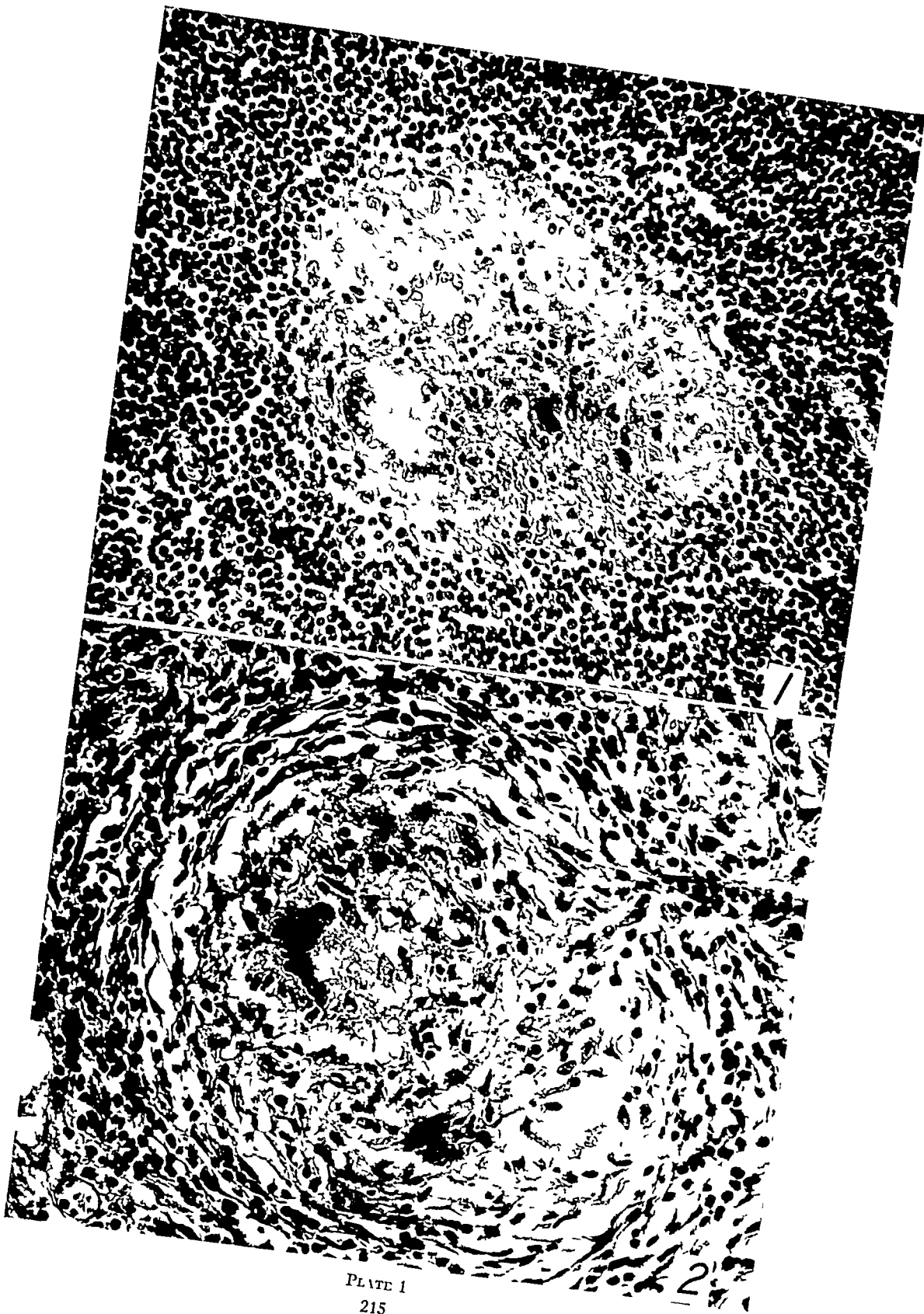
### PLATE 1

Fig 1 Section from peribronchial lymph node showing typical healing tubercle Note that lymphocytic infiltration of tubercle is no greater than in fig 2 This lymph node showed several such tubercles The remainder of the enlarged node was composed of closely packed lymphocytes similar to the condition surrounding the tubercle X 300

Fig 2 Healing tubercle from pulmonary tissue Note fibrosis and lymphocytic infiltration which is no different from a similar tuberculous lesion in a nonleukaemic individual X 300

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\* We are indebted to Dr Wm R Strutton who performed the necropsy



areas of fibrous tissue which were infiltrated to a greater or lesser extent with lymphocytes, no tubercle bacilli could be found in these regions

The peribronchial lymph nodes (figure 1) showed a few scattered tubercles with monocytes, giant cells and a moderate infiltration of lymphocytes. The tissue outside of the tubercles was closely packed with lymphocytes and there was a slight degree of infiltration of the capsules of the nodes with lymphocytes. A similar condition without tubercle formation was present in the mesenteric nodes.

Several sections of splenic tissue (figure 7) were examined and they all showed the pulp closely packed with lymphocytes. No evidence of tuberculosis was found. The malpighian corpuscles could be easily distinguished and did not appear to be involved in the leukaemic process. They appeared less cellular than the pulp.

The rib-marrow (figure 6) was very cellular and was devoid of fat. There were large irregular areas in which the cells were all of the lymphocytic type. Adjacent to and between such lymphocytic accumulations there was hyperplastic myelogenous tissue with the predominant cell being of the myelocytic type.

Sections of other tissues revealed nothing of particular note.

#### COMMENT

The coexistence in this case of typical lymphocytic leukaemia and of clinically active far-advanced pulmonary tuberculosis throws additional light upon the relation of leucocytes to the tuberculous process. The association of these two diseases is rare and according to Parker, *et al* "in our experience malignant lymphoma of other types (not Hodgkin's disease) is never associated with *active* tuberculosis". While our case shows that *active* pulmonary tuberculosis and lymphocytic leukaemia can be associated, such a condition must be very rare as we could find in the literature but one comparable case.

In our case it is impossible to state whether the diseases occurred

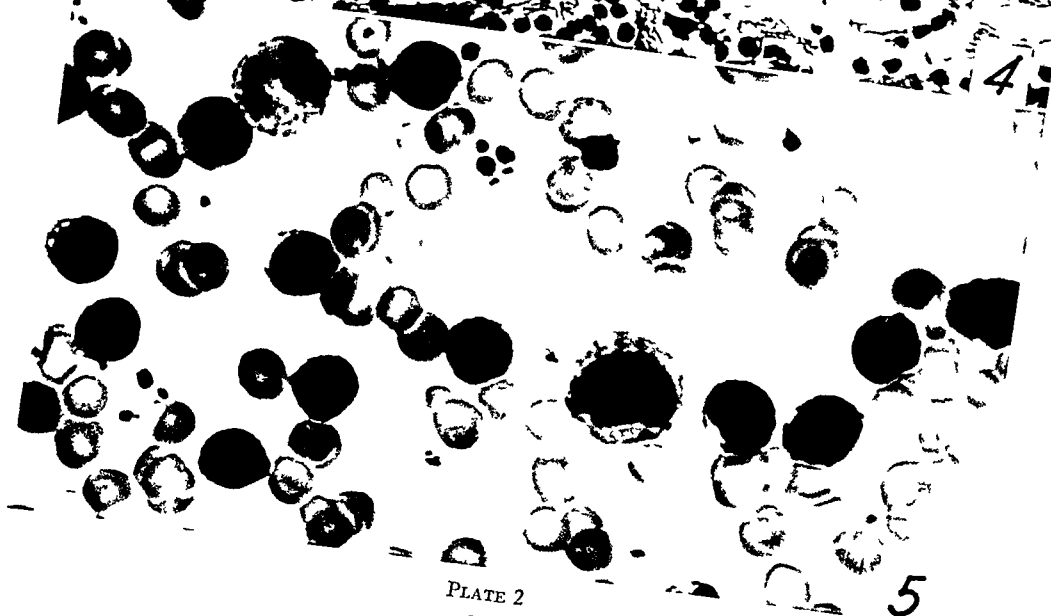
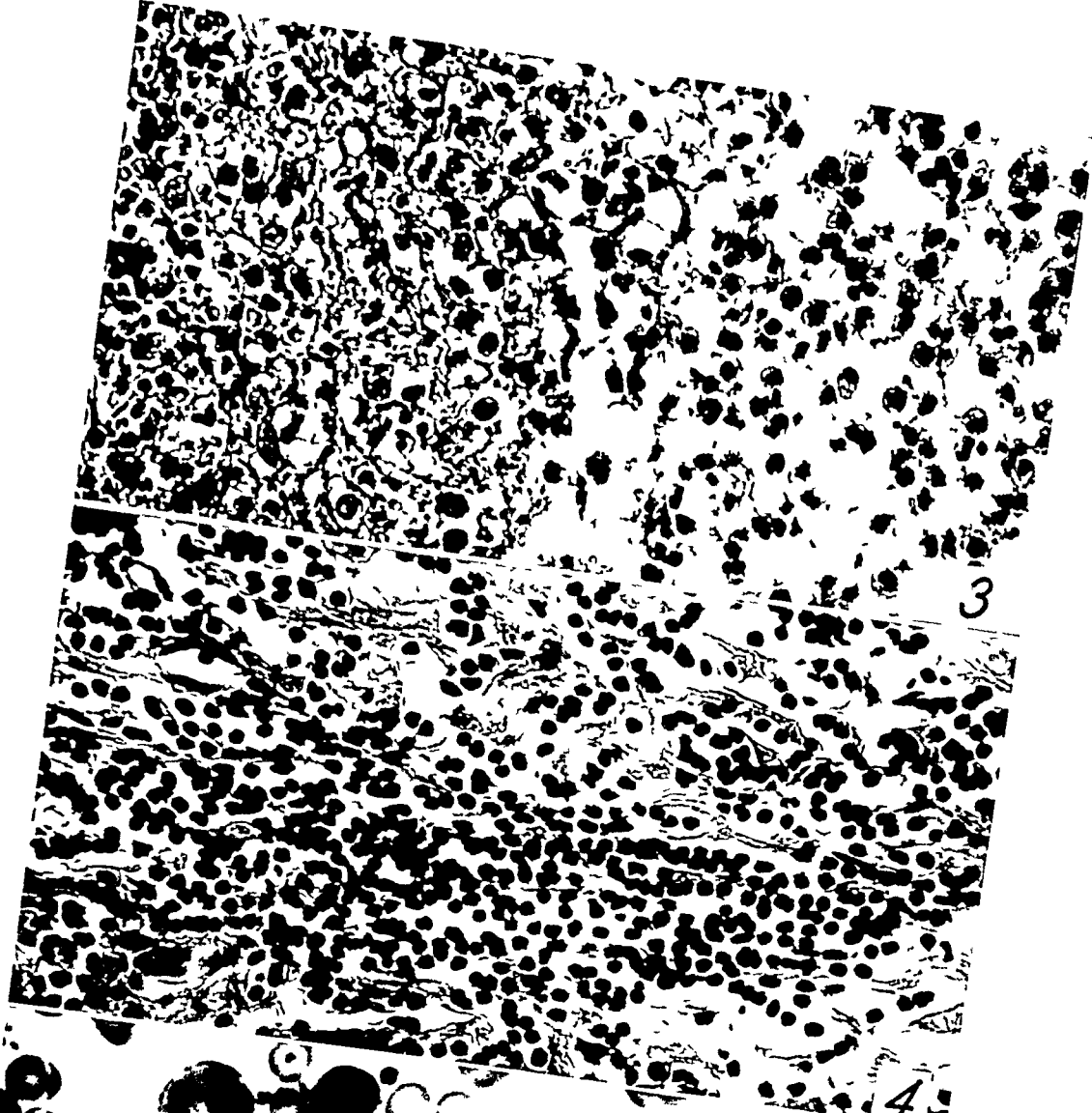
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#### PLATE 2

Fig 3 Inner wall of tuberculous cavity showing neutrophilic infiltration and fibrinous exudate. There were no lymphocytes in such locations. Tubercle bacilli were easily demonstrable in this purulent exudate.  $\times 500$

Fig 4 The outer portion of the thick cavity wall taken from same section of tissue as fig 3. Note fibrosis and abundant lymphocytic infiltration. In numerous areas the infiltration was even more intense than shown here. No other type of leucocyte was present and tubercle bacilli could not be demonstrated in such areas.  $\times 500$

Fig 5 Blood film showing general picture of the circulating blood. There are 12 typical lymphocytes, 1 monocyte and 1 nonsegmented neutrophile.  $\times 1000$



simultaneously or whether one followed the other. No aetiological relationship of the processes can therefore be determined.

It is well known that in uncomplicated tuberculous cases a high percentage of lymphocytes is a favorable sign, yet in this case such an interpretation of the leucocytic picture would be erroneous. The blood contained from fifty to over one hundred times as many lymphocytes as normal and still there was an active progressive pulmonary tuberculosis. In such a condition one may regard the lymphocytes as being abnormal in function and hence unable to participate in the tuberculous process. If one may judge by the presence of lymphocytic infiltration the majority of the tuberculous lesions did not differ essentially in this case from those in individuals without leukaemia. In some areas lymphocytic infiltration was so excessive that it appeared as if these cells were multiplying within the tuberculous foci. At least the lymphocytes were present in the same locations in the same type of tuberculous lesions as they are commonly found in uncomplicated tuberculosis. It is not possible to determine whether any abnormality of functional activity existed in these lymphocytes but at least they showed a tendency to immigrate to the locations where normal lymphocytes are commonly found.

Unless the lymphocytes in lymphocytic leukaemia are nonfunctional then this case suggests that a lymphocytosis *per se* is not of prime importance in tuberculosis. We do not believe that any of the leucocytes which participate in infectious lesions are attracted to the site of infection by the bacteria *per se*. Rather we believe that the chemical damage produced in the tissues by the presence and growth of the bacteria is what is responsible for the leucocytic invasion. The nature of chemical damage produced determines the type or types of leucocytic infiltration found. One of us (6) in a previous communication has suggested that the different phases of the pathogenesis of tuberculosis are reflections of changes in the chemical structure within the foci of inflam-

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#### PLATE 3

Fig 6 Rib marrow. Note solid sheet of lymphocytes in the upper part and of hyperplastic myeloid tissue in the lower portion of the picture. No evidence of tuberculosis was found.  $\times 500$

Fig 7 Section of spleen. Note that the pulp (right half of picture) is heavily infiltrated with lymphocytes. The malpighian corpuscles have larger cells and do not seem to be particularly involved. A part of a malpighian corpuscle is shown in the left hand side of the photograph. No evidence of tuberculosis was found in the spleen.  $\times 500$

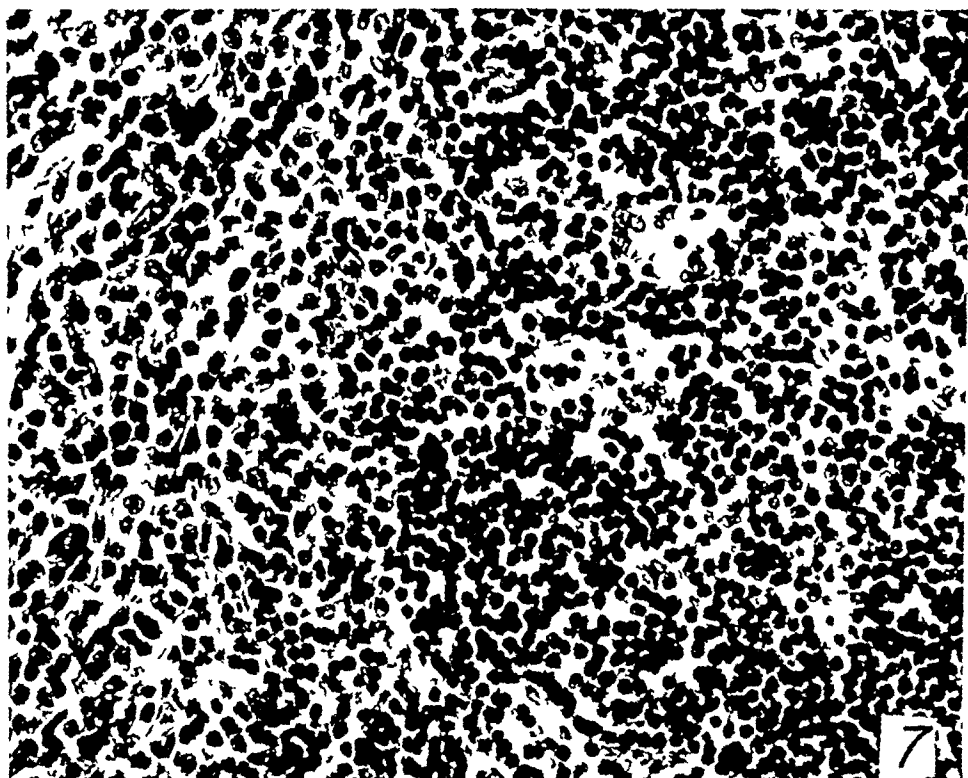
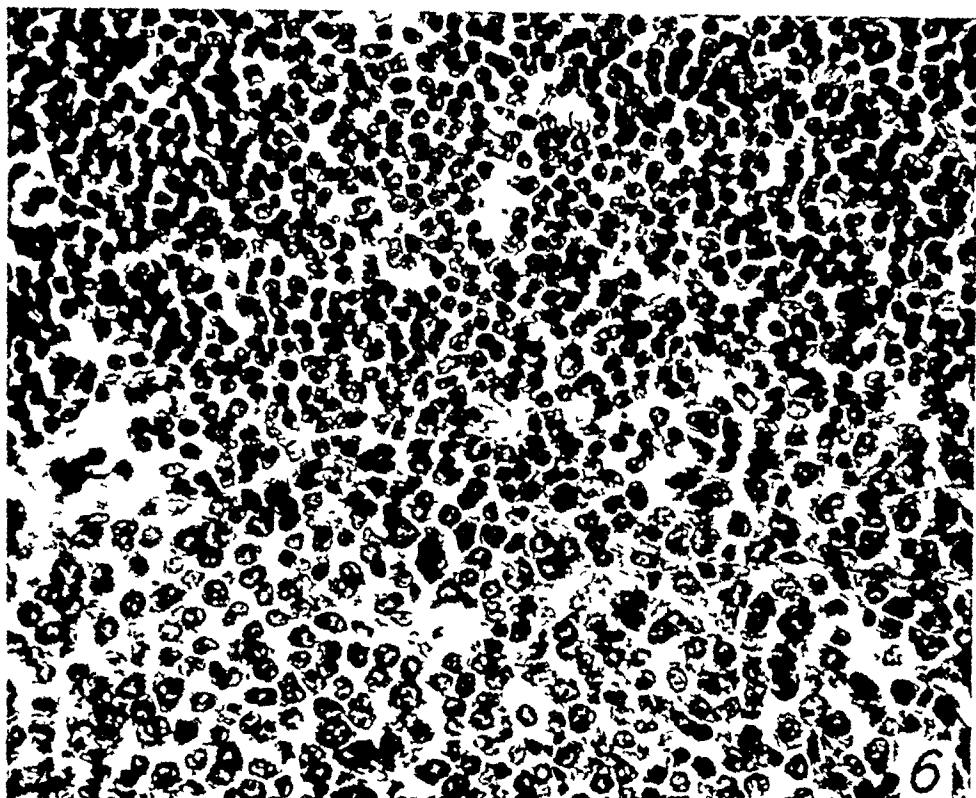


PLATE 3

mation In other words, the lymphocyte, monocyte or neutrophile invades an area because the type of chemical alteration at a given point is such that they are functionally adapted to counteract it If this be true then the case under discussion demonstrates the futility of attempts to produce artificial lymphocytosis in tuberculosis Unless a physico-chemical condition exists within a tuberculous lesion which attracts lymphocytes they will not migrate into it no matter how many may be available in the circulating blood

In previous communications (6) (7) one of us has stressed the part played by the neutrophile in certain phases of tuberculosis A superficial inspection of the leucocytic counts given in table 1 would seem to contradict our previous assertions, since in this case the neutrophiles made up but 2 per cent to 5 per cent of the leucocytes It will be noted however that in all but three counts the total number of neutrophiles was above 5,000, this being the upper limit of normal In the column for immature neutrophiles it will be noted that 50 per cent to 94 per cent were of the nonsegmented nucleus type Not only was the total number of neutrophiles increased but also the demand for neutrophiles was so great that there was a marked increase in the proportion of immature cells In two cases of uncomplicated chronic lymphocytic leukaemia one of us (E M M) had found the percentage of immature neutrophiles to be within normal limits Whether this would hold for all of the uncomplicated cases of this type we cannot say However, the marked difference between the leucocytic content of immature neutrophiles in the uncomplicated lymphocytic leukaemias we have studied and the case combined with tuberculosis is such that it seems reasonable to designate the active tuberculosis as the cause of the difference noted

A study of the pulmonary lesions revealed the presence of neutrophiles in the usual locations for such cells, that is, the inner wall of cavities and caseous foci Examination of the sternal bone-marrow showed myelogenous hyperplasia compatible with the circulating neutrophilic picture Linking the pulmonary lesions, the marrow reaction and the circulating leucocytic picture, ample evidence is obtained to warrant the conclusion that the neutrophile functioned in the case under discussion in the same way that it does in uncomplicated tuberculosis

The monocyte (total numbers) was also increased in the circulating blood and was found to be present in tuberculous lesions in the ordinary locations

A survey of the case as a whole showed that the lymphocytic leukaemia had not changed the essential pathological picture of the co-existing active tuberculosis from that usually found in uncomplicated tuberculous infection. The circulating blood picture indicated not only the presence of lymphocytic leukaemia but also a serious disease process in which the neutrophile and monocyte were involved. The demonstration of clinically active pulmonary tuberculosis rendered an intelligent pathological interpretation of the significance of the neutrophilic and monocytic picture possible.

#### SUMMARY

A case in which lymphocytic leukaemia and active pulmonary tuberculosis coexisted is reported.

The independence of the two disease processes is suggested. Despite the presence of a lymphocytic leukaemia the tuberculous pathology was essentially the same as is found in uncomplicated tuberculous infection.

The participation of the lymphocyte in the tuberculous process seems to be dependent upon the conditions (probably chemical) within a lesion. The mere presence of a large number of lymphocytes in the circulation seems to have little if any influence upon the pathological condition within an active, caseating and cavitating process.

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# THE EFFECT OF VITAMIN-A DEFICIENCY ON EXPERIMENTAL TUBERCULOSIS IN THE GUINEA PIG AND RABBIT<sup>1 2</sup>

MORRIS STEINER, MERIDIAN R. GREENE AND BENJAMIN KRAMER

## INTRODUCTION

The influence of complete or partial lack of vitamins in the diet on the course of infection produced by the tubercle bacillus has interested us. Previous work has indicated that chronic deficiency of vitamin C appears to hasten the development of experimental tuberculosis in the guinea pig, while a deficiency in vitamin D in rabbits seems to have no effect on the tuberculosis produced in this animal (1). Since the recognition by McCollum and Davis (1913) (2) of the existence of a fat soluble vitamin necessary for growth, much work has accumulated to indicate that vitamin A plays a rôle in the resistance of the body to infection. McCollum (1917) (3) first drew attention to the susceptibility of rats to respiratory infection when fed on diets deficient in fat soluble vitamin. Later, E. Mellanby (1919) (4) showed that puppies under similar dietetic conditions often develop bronchopneumonia. Green and Mellanby (1928) (5) in an attempt to differentiate the effects of vitamin D and those of vitamin A were able to show that rats on diets deficient in vitamin A alone, developed a high percentage of lethal infections. As a result of their work they gave the name "anti-infective" vitamin to vitamin A. Further work by Mellanby and Green (1929) (6) indicated that clinically the administration of diets rich in vitamin A had a beneficial influence both in the treatment and prevention of puerperal sepsis.

Wolbach and Howe (1928) (7) have shown that keratinization of normal epithelium occurs in the respiratory, alimentary and gastrointestinal tracts, in the eyes and periocular glands in guinea pigs on vitamin-A deficient diets. In view of this finding it has been suggested that bacterial invasion may occur because of the interference with the normal healthy structure of the mucous membranes.

In these experiments it was planned to investigate the influence of

<sup>1</sup> From the Pediatric Research Laboratory, the Jewish Hospital of Brooklyn, New York.

<sup>2</sup> This work was aided by a grant from Mead Johnson and Company.

vitamin-A deficiency in guinea pigs and rabbits infected with tubercle bacilli. Very little work has been done on experimental tuberculosis in guinea pigs and rabbits maintained on rations depleted of vitamin A. Smith (1923) (8) found no difference in the amount of tuberculosis in guinea pigs fed on a diet deficient in vitamin A and in control animals receiving codliver oil in addition to the basal diet. His basal diet apparently was deficient in both vitamins A and D. He was unable to show any beneficial effects as far as the tuberculous process was concerned in infected animals fed normal diets and those receiving codliver oil in addition. He later (1925) (9) showed that rats infected with tubercle bacilli on adequate diets were about one-sixth as tolerant to tuberculo-protein as the noninfected controls, whereas rats maintained on a vitamin A deficient diet and infected with tubercle bacilli were about one-fortieth as tolerant to tuberculo-protein as noninfected controls.

Finkelstein (1932) (10) followed the course of tuberculosis in albino mice which were on a vitamin-A deficient diet and then infected with a bovine strain of tubercle bacilli. The tuberculous process appeared to progress more rapidly in the vitamin deficient animals than in the controls.

Otero, Konnisch and Oetmayer (1931) (11) were able to show that tuberculosis did not develop in rats on an adequate diet nor on one deficient in vitamin A after inoculation with human or bovine strains of tubercle bacilli. However, when an avian strain of the tubercle bacillus was used, tuberculosis developed in both groups but the disease progressed more rapidly in the animals depleted of the vitamin.

The problem which presented itself was to secure animals in which manifest signs of vitamin-A deficiency could be produced and which also could be infected with tubercle bacilli. Wolbach and Howe (7) have shown that vitamin-A deficiency can be produced in the guinea pig, although it is doubtful whether xerophthalmia, the common clinical manifestation of this deficiency, develops. Xerophthalmia, however, can be produced in rabbits on vitamin-A deficient diets and, since both of these animals show marked susceptibility to tuberculous infection, these two animals were used. Although we were able to produce vitamin-A deficiencies in both of these animals, it was difficult to maintain them over a long period of time, because the experimental diet, although theoretically adequate as regards all the needed known dietary factors, was a diet foreign to this species, since both guinea pigs and rabbits are herbivorous animals. A further discussion of this factor will be presented below.

## PROCEDURE

*Animals* Guinea pigs and rabbits of various breeds were used All were obtained from the same farms

Two rabbits or 6 guinea pigs of the same sex were kept in a cage The cages were made of metal with a wire-mesh floor-screen over a removable tray Each week the cages were soaked in 5 per cent cresol solution and thoroughly scrubbed The temperature of the animal rooms, which were large and well ventilated, was maintained at 70-80°F for the guinea pigs and at 60°F for the rabbits

*The diet*

Vitamin-A deficient		Vitamin A	
	<i>per cent</i>		<i>per cent</i>
Rolled oats	20 0	Rolled oats	17 0
White corn meal	41 5	White corn meal	39 5
White mashed turnip	33 0	White mashed turnip	33 0
Brewer's yeast <sup>3</sup>	3 0	Brewer's yeast	3 0
Calcium carbonate	1 5	Calcium carbonate	1 5
Sodium chloride	1 0	Sodium chloride	1 0
Vioosterol <sup>3</sup> 15 drops per kilo of ration		Butter fat	5 0
		Vioosterol 15 drops per kilo	

Thirty-three gm of turnip were mixed with 67 gm of dry mixture Multiples of this proportion of the constituents were given, the amount depending upon the number of animals in a cage The dry mixture was prepared weekly and the turnips were ground twice a week and kept in the refrigerator The diet was fed *ad lib* Filter paper clippings were given for additional roughage Freshly distilled water was given daily and iodine solution was added to this once a week In addition, the guinea pigs were fed 5 cc of fresh orange juice 6 times weekly The amount of vitamin A in this quantity of orange juice did not prevent the condition of avitaminosis from developing and adequate protection against scurvy was assured It was not thought necessary to give the orange juice to the rabbit as this animal is apparently not susceptible to scurvy

A few guinea pigs were maintained on a diet normal for this animal This consisted of rolled oats, 3 parts, wheat bran, 1 part, sodium chloride, 1 per cent, and calcium carbonate, 1 5 per cent Alfalfa hay was provided Fresh cabbage leaves were given 4 times a week

The guinea pigs did not take kindly to the diet even though the basal diet supplemented with butter fat contained all the needed known die-

<sup>3</sup> Supplied through the courtesy of Mead Johnson and Company

tary factors It is doubtful if even those who could be made to take it would survive the normal life-span of a guinea pig The lack of sufficient roughage, as is usually supplied by hay, appears to be the chief obstacle in maintaining herbivorous animals on experimental diets in a normal manner Only those animals living after 5 weeks on the diet were used in the data of the experiment Until this time deaths occurred in equal numbers in both groups, the one receiving the vitamin and the one being deprived of this factor The mortality during this preliminary period was about 50 per cent The pathological findings of the experimental animals will be discussed later

Rabbits progressing normally on either the experimental or control diet frequently developed a sudden diarrhoea and died within a day or two As coccidia were usually found in the faeces, a latent infection was apparently flared up by the lack of sufficient roughage in the diet In spite of many attempts, no adequate substitute for hay could be made

*Tuberculin tests* At the onset of the experiment all guinea pigs gave negative dermal reactions when injected intracutaneously with 0.1 cc of 5 per cent Old Tuberculin Rabbits were not skin tested

*Infection of animals* The bovine strain, C3, obtained from the New York Department of Health, was used for inoculating the rabbits Weighed, normal saline suspensions of the organism grown for 2 weeks on Petroff's glycerine-egg media were used The guinea pigs were inoculated by the enteric route with sputum obtained from open cases of pulmonary tuberculosis

*Pathological procedure* Each animal was autopsied The scoring for tuberculosis was adapted from the method of Petroff and Steenken (1930) (12), the involvement being graded from 1-plus to 4-plus according to its extent and severity

After fixation in 4 per cent formalinized saline, sections were imbedded in paraffin, sectioned and stained by the hematoxylin-eosin method Sections were also stained for 45 minutes at 56°C in Neelsen's carbol-fuchsin and destained and counterstained in Gabbett's solution These were then examined for the presence of tubercle bacilli

*Statistical method* The weights and survival time were analyzed by a special statistical method (R. A. Fisher's *Statistical Method*, page 107, Oliver and Boyd, London, 1930) As the method has already been described in detail in the first paper of this series (1), it is sufficient to say that when the value of  $P$  is 0.1 or less the difference between the means of the comparable series is statistically significant

## PROTOCOLS OF THE EXPERIMENTS

*Group 1 Nontuberculous guinea pigs* Six animals on the diet deficient in vitamin A, 7 animals receiving the basal diet supplemented with the vitamin and 4 animals on a normal guinea-pig diet were used

TABLE 1

*Summary of statistical analysis of weights and survival periods in guinea pigs on vitamin-A deficient and control diets*

	WEIGHT MEAN IN GRAMS AT				SURVIVAL MEAN IN DAYS
	Onset	5 weeks	9 weeks	Death	
-A only	344	363	319	363	56
+A only	325	335	411	492	94
P	36	24	14	< 01	< 01
Nor only	327	514	598	671	100
+A only	325	335	411	492	94
P	> 9	< 01	< 01	< 01	
Nor tb*	332	403	479	514	79
Nor only	327	514	598	671	100
P	64	013	019	025	
Nor tb*	332	403	479	514	79
+A tb	325	346	369	339	81
P	503	023	< 01	< 01	
+A tb*	325	346	369	339	81
+A only	325	335	411	492	94
P	1 0	57	< 01	< 01	
-A tb*	345	349	311	305	68
-A only	344	363	319	363	56
P	> 9	46	83	706	12
-A tb*	345	349	311	305	68
+A tb*	325	346	369	339	81
P	01	82	< 01	11	< 01

-A = basal diet alone

+A = basal diet + 5 per cent butter fat

Nor = normal guinea pig diet.

\* = fed tuberculous sputum

P = statistic, significant when less than 01

*Pathology (a) Weights and survival period* Animals on a vitamin-A deficiency were maintained for 40 to 100 days when the experiment was terminated. As noted by Wolbach and Howe (1928) (7), the only ex-

ternal signs of the deficiency were a cessation of growth and weight loss. These animals died at a significantly earlier time than those receiving the supplemented basal diet. The guinea pigs depleted of the vitamin also weighed much less at death than their corresponding controls (table 1).

A second set of control animals (numbers 108-1,2,3,4) had been placed on a normal guinea-pig diet. These animals gained weight steadily and were in excellent health. They thrived better than the group on the basal ration supplemented with the vitamin. Their weights were significantly greater from the third week to the termination of the experiment when both series were killed (table 1).

(b) *The deficiency* All sections of the trachea of guinea pigs on the vitamin depleted diet showed either a complete or partial replacement of the normal columnar epithelium by the squamous type of cell. In the series of 6 animals, the pelvis and ureters of two were swollen, thickened and contained a gritty and pasty material. A bilateral hydronephrosis resulted. The bladder contained similar masses and the walls were thicker than normal. These findings did not occur in the animals receiving vitamin A. Cloudy swelling of the cornea as described by Boock and Trevan (1922) (13) was not found in these animals nor in the larger experimental group that follows.

(c) *Intercurrent infections* Five of 6 animals on the depleted ration showed pneumonia at autopsy. This finding occurred in 2 of 7 animals on the ration supplemented with butter fat and in none of 4 on the normal herbivorous diet. These uninoculated animals were in the same room but not in the same cages with tuberculous guinea pigs and no cross infection resulted.

(d) *Summary* Animals on the diet depleted of the vitamin died significantly earlier than those receiving this factor, and pneumonia was present in most cases of the avitaminosis. The vitamin-A deficient guinea pigs showed keratinization of the tracheal epithelium, two showed hydronephrosis.

*Group 2 Tuberculous guinea pigs* Twenty-five guinea pigs on the basal diet, 22 on the same ration supplemented with 5 per cent butter fat as the source of vitamin A and 18 on a normal guinea-pig ration were fed 25 cc of heavily infected sputum 5 times weekly with a tuberculin syringe. Feeding was begun when they were placed on their respective rations.

(a) *Weight and survival period of normal diet animals* Tuberculous

animals on a normal guinea-pig diet weighed significantly less than non-infected animals on normal diets. The survival period was not calculated as the tuberculous animals were killed at various periods for pathological study.

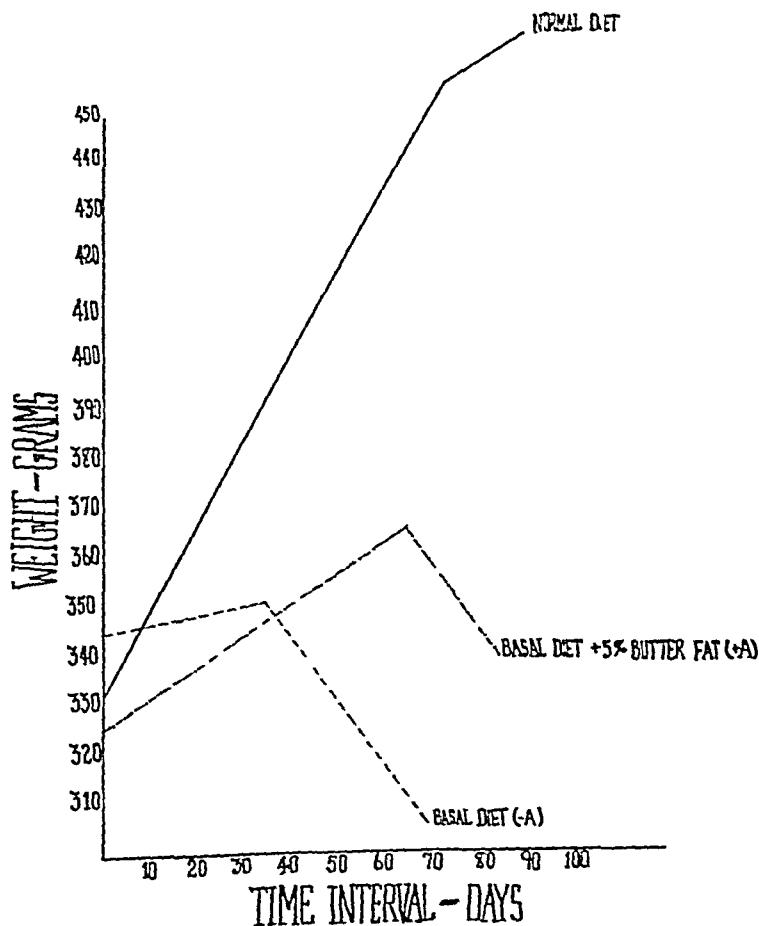


CHART 1 Mean average weights of tuberculous guinea pigs on normal diet, basal diet + 5 per cent butter fat (+ A), basal diet alone (- A)

(b) *Weight and survival period of experimental animals* Tuberculous animals on the basal diet supplemented with 5 per cent butter fat weighed significantly more than tuberculous animals on the basal diet. At 5 weeks there was no significant weight difference but at 9 weeks the control animals weighed more. There was a significant difference in

weights between the infected animals receiving the basal diet and 5 per cent butter fat, and the infected animals on a normal diet, the latter animals weighing more at the end of the experiment

The mean average survival period of the vitamin-A deficient animals was 68 days while that of those receiving the 5 per cent butter fat was 81 days. This difference in survival period was significant since  $P$  was less than .01. However, there was no significant difference in the survival period between the infected and noninfected animals on the deficient diet (table 1).

(c) *The deficiency* Metaplasia of the normal columnar tracheal epithelium occurred in most of the vitamin-A deficient guinea pigs. Sixteen of 25 animals had dilatation of the upper portion of the ureters and pelves. In some, calculi were found. These were usually present in the upper portion of the ureter and pelvis. In several cases unilateral or bilateral hydronephrosis occurred. A more extensive study of this condition is now being undertaken (table 2).

(d) *Secondary infections* Seventeen of 25 infected, depleted guinea pigs showed pneumonia at autopsy as compared with 3 of 22 animals in the control group.

(e) *Tuberculosis* Eleven out of 21 animals (52 per cent) receiving the diet deficient in vitamin A had generalized tuberculosis, while 10 out of 21 control animals (48 per cent) on the basal diet plus 5 per cent butter fat showed similar involvement. (Animals 93-1 and 5, 95-3 and 98-5 were not included in the tuberculosis score as they lived less than 45 days and died of secondary pneumonia.) Histological study showed the same type of involvement in both groups but, as pointed out above, the vitamin-A deficient animals had a significantly shorter survival period than their corresponding control animals. When the experimental period was subdivided into 2 periods of 60 to 80 days and 80 to 100 days, it was found that 6 of 15 vitamin-A deficient animals had generalized tuberculosis as compared with 5 of 10 control animals in the first period, whereas in the second period (80 to 100 days) 5 out of 6 deficient animals had generalized tuberculous involvement as compared with 5 out of 12 control animals. Apparently, the lack of vitamin A did not hasten the development of tuberculosis in the animals succumbing early in the experiment.

In the third group of tuberculous animals, that is, those fed on a normal guinea-pig diet and infected with tuberculous sputum, only 5 out of 18 animals (27 per cent) had generalized tuberculosis as compared



TABLE 2

*Autopsy findings in kidneys and trachea of vitamin A deficient and control animals*

ANIMAL NUMBER	KIDNEY (GROSS)	EPITHELIUM TRACHEA (MICROSCOPIC)	SURVIVAL IN DAYS
Experimental			
92-1	Early bilateral hydronephrosis	—	61
92-2	0	Squamous	62
92-3	Early unilateral hydronephrosis	Modified columnar	89
92-5	Bilateral hydronephrosis, gritty material in pelvis	Squamous	60
92-6	Bilateral hydronephrosis	Squamous	71
93-1	0	Modified columnar	43
93-3	Bilateral hydronephrosis	Squamous	75
93-4	Bilateral hydronephrosis, gritty material in pelvis	Squamous	71
93-5	0	Modified columnar	46
94-1	Left ureter slightly swollen	—	86
94-4	Very early hydronephrosis	—	67
94-5	0	—	64
95-1	Bilateral hydronephrosis, putty like masses in pelvis, upper portion of ureter markedly swollen	—	62
95-2	Bilateral hydronephrosis	Squamous	87
95-3	0	Columnar	42
95-5	0	Columnar	41
96-2	Unilateral hydronephrosis	Squamous	72
96-3	0	Modified columnar	61
96-4	0	—	77
96-5	Beginning hydronephrosis, gritty material in right ureter	—	100K
96-6	Beginning hydronephrosis, gritty material in both pelves	Modified columnar	99K
97-1	0	Squamous	57
97-2	Bilateral hydronephrosis	—	94
97-4	Early bilateral hydronephrosis—upper $\frac{1}{2}$ both ureters swollen	—	69
97-6	Bilateral hydronephrosis, gritty material in pelvis and upper ureter	Squamous	58
Controls 98-1 to 102-6	0	Columnar	81

— = mucosa unsuitable for microscopic study

K = killed

Experimental = vitamin A deficient animals

to 11 out of 21 vitamin-A deficient animals and 10 out of 21 control animals (basal diet + 5 per cent butter fat) The animals in this group

TABLE 3A  
Relative amount of tuberculosis and survival time in vitamin deficient and control guinea pigs

ANIMAL NUMBER	LUNG	LIVER	SPLEEN	SMALL INTESTINE	CAECUM	COLON	GROSS TISSUE SCORE	SURVIVAL
Experimental								
92-1	1+	3+	2+	0	0	0	3+	61
92-2	1+, Pn	0	1+	0	0	0	1+	62
92-3	2+, Pn	3+	3+	0	0	0	4+	89
92-5	1+, Pn	0	0	2 ulcers*	0	0	1+	60
92-6	1+, Pn	2+	3+	0	0	0	3+	71
93-1	0, Pn	0	0	0	0	0	0	43
93-3	0, Pn	2+	2+	0	0	0	2+	75
93-4	0, Pn	2+	1+	1+	0	0	2+	71
93-5	0, Pn	2+	0	0	0	0	2+	46
94-1	0, Pn	2+	1+	0	0	0	3+	86
94-4	1+	3+	3+	0	0	0	2+	67
94-5	2+, Pn	0	1+	1+	0	0	1+	64
95-1	0, Pn	0	1+	1+	0	0	1+	62
95-2	3+, Pn	0	2+	0	0	0	0	42
95-3	0	1+	1+	0	0	0	0	41
95-5	0, Pn	0	0	2+	0	0	2+	72
96-2	0, Pn	0	0	0	0	0	4+	61
96-3	0, Pn	2+	0	0	0	0	4+	77
96-4	1+, Pn	2+	0	0	0	0	3+	100K
96-5	2+	4+	3+, 3+	0	0	0	3+	99K
96-6	3+, Pn	3+	1+	0	0	0	4+	94
97-1	2+	3+	3+, 2+	0	0	0	3+	69
97-2	4+, Pn	2+	0	0	0	0	3+	58
97-4	3+, Pn	2+	2+	0	0	0	4+	96K
97-6	1+	2+	0	2+	0	0	1+	94K
98-1	3+, Pn	1+	1+	0	0	0	2+	75
98-2	3+	4+	4 ulcers	3+	0	0	1+	96K
98-3	0	0	0	3+	0	0	1+	94K
98-4	1+, Pn	1+	3+, 2+, 1+	0	0	0	1+	96K
98-5	1+	0	3+, 3+, 2+	0	0	0	0	39
99-1	0, Pn	0	0	0	0	0	1+	67K
99-2	1+	0	1+	0	0	0	4+	62K
99-3	3+	1+	1+	0	0	0	3+	71K
99-5	1+	4+	1+	0	0	0	1+	88K
99-6	1+	3+	1+	0	0	0	3+	88K
100-2	1+	2+	2+	1+	0	0	1+	67K
100-3	0	2+	0	0	0	0	4+	62K
100-4	0, Pn	2+	0	0	0	0	3+	71K
101-1	2+	1+	3+	0	0	0	1+	88K
101-2	1+	4+	0	3+	0	0	3+	88K
101-3	0	1+	1+	0	0	0	1+	67K
101-4	0	1+	3+, 2+	0	0	0	4+	78K
101-5	1+	2+	3+	0	0	0	2+	78K
102-1	0	2+	0	0	0	0	2+	62K
102-2	2+	3+	0	0	0	0	2+	88K
102-3	2+	4+	3+	0	0	0	2+	88K
102-6	2+	3+	0	0	0	0	3+	71K
Control	1+	2+	1+	0	0	0	4+	95K
98-1	3+	1+	1+	0	0	0	4+	93
98-2	3+	1+	1+	0	0	0	2+	97K
98-3	0	4+	1+	0	0	0	3+	99K
98-4	1+, Pn	0	4 ulcers	3+	0	0	3+	
98-5	1+	2+	0	3+	0	0	3+	
99-1	0, Pn	1+	3+, 2+, 1+	0	0	0	3+	
99-2	1+	0	3+, 3+, 2+	0	0	0	3+	
99-3	3+	1+	0	0	0	0	3+	
99-5	1+	4+	1+	0	0	0	3+	
99-6	1+	3+	1+	0	0	0	3+	
100-2	1+	2+	2+	1+	0	0	3+	
100-3	0	2+	0	0	0	0	3+	
100-4	0, Pn	2+	0	0	0	0	3+	
101-1	2+	1+	3+	0	0	0	3+	
101-2	1+	4+	0	3+	0	0	3+	
101-3	0	1+	1+	0	0	0	3+	
101-4	0	1+	3+, 2+	0	0	0	3+	
101-5	1+	2+	3+	0	0	0	3+	
102-1	0	2+	0	0	0	0	3+	
102-2	2+	3+	0	0	0	0	3+	
102-3	2+	4+	3+	0	0	0	3+	
102-6	2+	3+	0	0	0	0	3+	
Control	1+	2+	1+	0	0	0	3+	

\* Tubercle bacilli found, Pn = pneumonia, experimental = vitamin A deficient animals, control = basal diet + 5 per cent butter fat  
System of scoring explained in text

were killed so that their survival period would correspond to the vitamin-A deficient group. The nutritional status of these animals was far superior to that of both experimental groups.

In the intestinal tract, 13 of 21 depleted guinea pigs had tuberculous lesions. These were present mostly in the ileum. One animal had tuberculous ulcer in this region and a second showed an area of ulceration in the caecum. Among the control group the incidence of lesions was the same but there was slightly more involvement in the caecum and colon. One animal receiving the vitamin had four ulcers in the small

TABLE 3B

*Relative amount of tuberculosis in guinea pigs fed normal diets infected by sputum*

ANIMAL NUMBER	LUNGS	LIVER	SPLEEN	SMALL INTESTINE	CAECUM	COLON	GROSS TR. SCORE	SURVIVAL TIME
103-1	1+	0	3+	0	0	0	2+	62K
103-2	2+	0	2+	3+	0	0	2+	99K
103-3	+	0	+	2+	0	0	2+	67K
103-4	+	0	2+	0	0	0	2+	78K
103-5	2+	3+	+	0	0	0	3+	71K
103-6	2+	+	3+	+	0	0	3+	99K
120-1	2+	0	+	+	0	0	2+	70K
120-2	0	0	+	0	0	0	1+	70K
120-3	0	0	+	0	0	+	+	87K
120-4	0	0	0	+	0	0	1+	77K
120-5	0	0	0	0	0	0	0	65K
120-6	0	0	+	0	0	0	1+	74K
143-1	Pn	4+	2+	3+	+	0	4+	66
143-2	0	0	0	0	0	0	1+	73K
143-3	2+	2+	2+	0	0	0	3+	73K
143-4	0	0	2+	+	0	0	1+	91K
143-5	4+	2+	3+	2+	0	0	4+	91K
143-6	0	0	+	0	0	0	1+	91K

K = killed

intestine. However, the involvement of the intestines for the most part consisted of early or moderately advanced tubercles.

In the group of animals on the normal guinea-pig diet, 8 out of 18 animals had definite gross intestinal lesions, 2 of which were advanced, but no gross ulcers were found (tables 3 A and B).

*Group 3 Nontuberculous rabbits* Seven rabbits receiving the diet supplemented with vitamin A and 3 animals on the basal diet alone were used.

*Pathology* The animals on the vitamin-A deficient ration had a

TABLE 4

*Significance of the mean weights of comparable groups of rabbits in vitamin-A experiment*

GROUP	TIME	WEIGHT MEAN (GMS)	DIFFERENCE	t	n	P
-A +A	Onset	1043 1049	6	27	8	79
-A +A	3 weeks	828 1153	325	5 81	8	< 01
-A +A	6 weeks	970 1278	308	3 16	8	014
-A +A	Death	1003 1396	293	1 5	8	16
-A -A tb	Onset	1043 1092	49	7 92	11	44
-A -A tb	3 weeks	828 1033	205	3 66	11	< 01
-A -A tb	6 weeks	970 1012	42	42	11	68
-A -A tb	Death	1003 990	13	13	11	89
+A +A tb	Onset	1049 1096	48	97	15	34
+A +A tb	3 weeks	1153 1021	132	1 61	15	13
+A +A tb	6 weeks	1278 1137	141	1 59	15	14
+A +A tb	Death	1396 1158	238	1 06	15	306
-A tb +A tb	Onset	1092 1096	4	09	18	> 9
-A tb +A tb	3 weeks	1033 1021	12	17	18	86
-A tb +A tb	6 weeks	1021 1137	125	63	18	53
-A tb +A tb	Death	990 1158	168	2 01	18	052

-A = animals on basal diet (vitamin A deficient)

+A = animals on basal diet + 5 per cent butter fat

tb = infected intravenously with 000,5 mgm of strain C3

P = statistic, usually significant when less than 05

The values t and n have been explained in detail in our first paper under "Statistical method," *Amer Rev Tuberc*, 1936, 33, p 588

weight mean significantly less than that of animals receiving this factor at 3 and 6 weeks on their respective rations. Both groups were killed at the end of the experimental period of 61 days (table 4). One animal on the basal diet showed xerophthalmia. No metaplasia of the epithelium of the trachea was noted on histological examination.

*Group 4 Tuberculous animals* Ten rabbits were placed on the deficient ration and 10 on the diet containing vitamin A. They were then inocu-

TABLE 5

*Autopsy findings in rabbits inoculated with 000,5 mgm of the C3 strain of tubercle bacilli*

ANIMAL NUMBER	LUNG	LIVER	SPLEEN	KIDNEY	GROSS TB SCORE	SURVIVAL
<b>Experimental</b>						
a1	4+*	2+*	3+*	1+*	4+	61
a2	4+*	1+*	1+	1+*	3+	62
a3	4+*	2+*	3+*	2+	4+	61
a4	4+*	0	0	1+*	3+	45D
a5	3+*	0	1+*	0	3+	45D
a6	4+*	1+*	4+*	1+*	4+	58D
a7	4+*	2+	4+	2+	4+	62
a8	3+*	2+*	2+*	1+*	4+	61
a9	4+*	0	3+*	0	3+	50D
a10	3+*	2+	2+*	0	4+	43D
<b>Control</b>						
a21	2+*	1+*	1+*	0	3	54D
a22	4+*	0	2+*	2+	3	61
a23	3+*	2+*	2+	1+	4+	61
a24	1+	0	2+	0	1+	46
a25	3+	1+*	2+	—	4+	46'
a26	2+*	1+*	1+*	0	3+	42D
a27	2+*	0	1+*	—	2+	62
a28	4+*	2+	2+*	1+*	4+	62
a29	4+*	2+*	2+*	1+	4+	60
a30	2+*	0	2+*	2+*	2+	62

\* Tubercle bacilli found, D = died, others killed. Animals 11-13 uninoculated experimental group, negative for tuberculosis as well as animals 14-20, uninoculated controls.

lated intravenously with 000,5 mgm of C3, a bovine strain of tubercle bacillus.

*Pathology (a) Weights and survival period* Tuberculous rabbits on the diet deficient in vitamin A lost significantly more weight than those on the control diet. As some of the control rabbits were killed when the deficient animals died and all surviving were killed at 61 days, the survival period could not be calculated. Five of 10 tuberculous animals on

the vitamin-A depleted ration died before the end of the experiment. Infected animals on the diet deficient in vitamin A lost significantly more weight than tuberculous control rabbits. There was likewise a significant weight difference at 3 and 6 weeks between uninfected animals depleted of vitamin A and those on the supplemented ration. The weight difference between infected and uninfected vitamin-A deficient rabbits or between infected and uninfected control animals was not significant (table 4).

(b) *The deficiency* Two animals (a4 and a6) developed very definite xerophthalmia and one (a9) had an early stage of this condition when it died of coccidiosis. This did not occur in rabbits receiving vitamin A.

(c) *Secondary infections* Secondary pneumonias were not present in deficient or control animals. It should be recalled that the experiment was terminated at 61 days. Over 50 per cent of the animals died before they were on the diets 6 weeks, usually from a sudden diarrhoea which was caused by coccidiosis in most instances. Only those animals who lived longer than 6 weeks were included in our data.

(d) *Tuberculosis* In the group on the diet producing xerophthalmia, all 10 rabbits developed very advanced tuberculosis, while 7 of 10 control animals had tuberculosis of similar severity. All of the depleted animals had extensive caseous pneumoma, this occurred in only 5 out of 10 rabbits on the supplemented ration. None of the latter animals had lesions of 3 plus or greater severity in the spleen, but 5 of 10 animals in the condition of avitaminosis had tuberculosis of this extent. Tuberculous involvement of the kidney, liver and bone marrow was about the same in both groups (table 5). Intestinal sections showed no tuberculosis.

#### DISCUSSION

Guinea pigs on a diet deficient in vitamin A showed metaplasia of the normal columnar epithelium to the squamous type as described by Wolbach and Howe (1928) (7). They frequently developed dilatation of the ureters and pelvis, in some cases hydronephrosis and small white calculi were found. This condition was first described by Osborne and Mendel in rats (1917) (14). The presence of respiratory infections in vitamin-A depleted animals has been described by numerous investigators (see reviews by Clausen, 1934 (15) and Robertson, 1934 (16)). We found secondary pneumonias to be prevalent in the guinea pigs on the ration deficient in this factor. The animals not receiving vitamin A had

a mean weight and survival period significantly less than those on the basal diet supplemented with the vitamin. However, it is important to note that although these control animals received a diet theoretically adequate in nutritional requirements they had weights definitely lower than those of guinea pigs on a normal diet for this species and few looked as well. Herbivorous animals are accustomed to a large amount of roughage, usually in the form of hay, and this factor is apparently very important in maintaining a condition of physical well-being and maximum growth.

Tuberculous guinea pigs on the vitamin-A deficiency did not die sooner than animals on the deficiency alone nor did they weigh less. Apparently, the added burden of the infection could not further reduce the poor physical condition of the animals caused by the vitamin deficiency. The deficiency evidently caused the death of many of the tuberculous guinea pigs.

The incidence of generalized tuberculosis developing during the experiment was about 50 per cent in the animals not receiving the vitamin and also in those whose basal diet was supplemented with this factor. Although the survival period of the vitamin-A deficient animals was significantly shorter than those on the control diet, an analysis of the animals dying earlier in the experiment, that is, 60 to 80 days, did not show any greater incidence of advanced tuberculosis in the former group of animals. It was, therefore, felt that the tuberculous process was not accelerated in the deficient animals.

When the tuberculosis in the guinea pigs receiving the basal diet supplemented with vitamin A was compared to that in the group of similarly infected animals fed on a normal ration for guinea pigs, the incidence of advanced tuberculosis was much greater in the former group of animals. The unnatural physical form of the experimental diet, although adequate in all the known nutritional factors, apparently lowered the resistance of the animals to some extent. The absence of sufficient roughage in the experimental diet may also account for the greater absorption of organisms ingested in this group, as compared to that in the animals on the normal guinea-pig diet, which were fed large amounts of hay.

It was difficult to correlate the findings in this experiment with those obtained in our previous investigation with vitamin C. Our guinea pigs on the vitamin-C deficient diet supplemented with orange juice were maintained in excellent health for a prolonged period. As already mentioned, animals on the vitamin-A depleted diet supplemented with

butter fat were not so maintained. When sputum was fed to animals on the diets just mentioned, those on the diet with vitamin A had more generalized tuberculosis than the vitamin-C control guinea pigs.<sup>4</sup> This was even more striking since the mean survival time of the animals in this experiment was 81 days and that of the guinea pigs on the vitamin-C control ration was 142 days. When infected vitamin-A deficient animals were compared with infected animals on the diet of chronic scurvy, the latter had more generalized tuberculosis. However, the mean survival period of the animals depleted of vitamin A was only 68 days and that of the chronic scorbutic animals was 119 days.

Rabbits were inoculated with a small dose of strain C3 which proved to be very virulent. Extensive advanced tuberculosis developed in a short time and animals were killed as it was feared any difference caused by the vitamin deficiency might be masked. The incidence of advanced tuberculosis appeared to be slightly greater in the animals on the depleted ration. These animals seemed to have a definitely greater involvement in the lungs and spleen but, due to the small number of rabbits surviving long enough to be included in our data, accurate analysis is not possible. With a much larger series and a less virulent strain of tubercle bacilli, it might be possible to establish these findings definitely.

#### CONCLUSIONS

1 Guinea pigs and rabbits receiving a vitamin-A depleted basal diet supplemented with vitamin A could not be maintained in excellent health as were those receiving their respective normal diets.

2 Vitamin-A deficiency caused a significant lowering in body weight as compared to that of animals on the basal diet with added vitamin A.

3 Vitamin-A depleted guinea pigs survived for a shorter period than animals receiving the vitamin.

4 Pneumonia occurred in a high percentage of guinea pigs depleted of vitamin A.

5 Dilatation and swelling of the ureters with calculus formation were found in some of the guinea pigs on the diet producing avitaminosis.

6 The development of tuberculosis did not appear to be accelerated in vitamin-A deficient guinea pigs, especially those surviving from 60 to 80 days after infection.

7 Tuberculosis did not further reduce the weights nor the survival span of guinea pigs depleted of vitamin A.

<sup>4</sup> Vitamin C control guinea pigs were animals on scorbutic basal diet plus orange juice.



8 Tuberculous infected guinea pigs on a basal diet supplemented with all the known food factors developed more extensive lesions than similarly infected animals on a normal ration for this animal

9 Rabbits on a diet deficient in vitamin A appeared to develop slightly more extensive tuberculosis in the lung than control animals, when inoculated intravenously with strain C3

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# THE SEDIMENTATION RATE AND MEDLAR'S INDEX<sup>1,2</sup>

A Comparison

A R MASTIN

The blood is a sensitive reflector of alterations occurring anywhere in the body. Throughout life there is a constant interchange taking place between the blood and the other body tissues. This interchange produces continued variations in the composition of the blood both in its liquid and solid constituents. In spite of these constant variations a number of adaptive processes cooperate in maintaining an equilibrium, which in health gives the blood a uniform composition in both its histological structure and its chemical composition. Disease conditions usually destroy this normal equilibrium with the production of definite changes, which, when rightly interpreted, give valuable information regarding the underlying pathology.

For many years efforts have been made to establish a characteristic blood picture which would be helpful in evaluating the underlying pathology in tuberculosis. The establishment of such a picture would, it was thought, be of inestimable value to the clinician since it would enable him to determine with greater accuracy both the extent of the lesion and the course it was pursuing, and at the same time give definite information regarding the effectiveness of treatment. In regard to treatment it was hoped that such a picture would be of great aid in determining the time when any particular type of treatment should be instituted as well as the length of time it should be maintained. These objectives have been attained to a considerable degree by studies of both the corpuscular and plasma content of the blood. To-day important information regarding a tuberculous lesion can be derived from the white blood-picture as exemplified in Medlar's leucocytic index, and from the plasma-corpuscular relationship shown by the red-cell sedimentation rate.

Studies to determine the significance of leucocytic changes occurring

<sup>1</sup> From the Lutheran Sanitarium, Wheat Ridge, Colorado

<sup>2</sup> Read at a meeting of the Denver Sanatorium Association, Denver, Colorado, May 26, 1936

in the blood of tuberculous patients began years ago. In 1905 Ullom and Craig (1) came to the conclusion that an increase of resistance to a tuberculous infection was accompanied by a corresponding increase in the number of lymphocytes in the blood. In 1925 Sabin, Cunningham and their coworkers (2) found that the course of a tuberculous lesion could be quite accurately followed by noting the relative proportions of monocytes and lymphocytes in the circulating blood in rabbits. It was found that when the monocyte-lymphocyte ratio was low, that is, when there was an increase in the monocytes, autopsy always disclosed an extensive and active lesion. On the other hand when the lymphocytes showed an increase, that is, when the monocyte-lymphocyte ratio was high, autopsy consistently showed an attenuated or arrested lesion. In 1926 Medlar (3) began an extensive study of the leucocytic reaction in tuberculosis. From his studies he arrived at the conclusion that there are three definite leucocytic types which are produced by tuberculous lesions at different stages of the pathological process. The neutrophils, he says, predominate in the phase of abscess-formation, of cavitation and of ulceration. The lymphocytes are the chief cells concerned with the healing process, and the monocytes increase when extension of the tuberculous lesion takes place. In 1935 Crawford (4) in conjunction with Medlar, devised a calculator for correlating Medlar's three types of cell reaction into one index number, which he calls the leucocytic index. In this paper this index is referred to as Medlar's index.

The value of the plasma-corpuscular relationship as shown by the red-cell sedimentation rate has been amply demonstrated since 1921 when Westergren (5) first urged the use of this valuable test in tuberculosis. In previous papers (6) (7) we showed that the sedimentation rate is an efficient method of determining the activity and of following the course of tuberculosis. In this paper the sedimentation rate refers to the percentage of fall of the red-cells in a two-hour period as determined by use of the modified Westergren technique described in the aforementioned articles (6) (7).

The present study was made in order to determine a relationship, if any, between the sedimentation rate and Medlar's index. The accuracy of the two tests in reflecting the clinical course of tuberculosis was investigated also, although the number of patients having coincident blood counts and sedimentation tests was found to be rather small for accurate statistical analysis. In spite of this drawback, however, several interesting relationships were discovered and it is hoped that further study will lead to their eventual confirmation.

In 1930 we began making sedimentation tests on all patients entering this institution so that we now have records of 158 consecutive tuberculous patients showing complete blood counts and sedimentation rates, together with a classification into minimal, moderately advanced and far advanced cases as determined by history, physical examination and X-ray. In this series there were 18 minimal, 35 moderately advanced and 105 far advanced patients. These groups showed a definite and parallel increase in their median sedimentation rate and Medlar index as shown in the following:

	<i>Minimal</i>	<i>Moderately Advanced</i>	<i>Far Advanced</i>
Median sedimentation rate	20	31	44
Median Medlar index	23	26	36

There is a definite correlation between the two tests, a high sedimentation rate and a high Medlar index closely paralleling extensive disease. Conversely a low sedimentation rate and a low Medlar index accompany a slight lesion.

The 158 patients were next grouped according to their progress in the sanatorium, that is, into those who improved, those who remained stationary or grew worse, and those who died. The number of patients in each of these groups was 111, 27 and 20 respectively.

	<i>Improved</i>	<i>Stationary and Worse</i>	<i>Died</i>
Median sedimentation rate	34	38	47
Median Medlar index	32	36	41

From these findings it appears that both tests have a definite relationship with the extent of the disease, for it is well known that the smaller amount of tuberculous involvement when treatment is started the greater is the probability of cure. Likewise it is evident that the lower the sedimentation rate and Medlar index the greater are the chances for improvement. Conversely the higher the sedimentation rate and Medlar index the worse is the prognosis.

The change which occurs in the sedimentation rate and Medlar index during the course of tuberculosis was studied in 65 far-advanced patients who had blood counts and sedimentation tests made concurrently several times during their stay in the sanatorium. It was found that in 77 per cent of these patients the sedimentation rate followed the clinical course of the disease. Medlar's index followed the clinical course in 58 per cent of the same patients. In 57 per cent of the patients the sedimentation rate and Medlar's index followed the clinical





# PRECIPITATION OF WATER SOLUBLE TUBERCULO- PROTEIN BY HYDROGEN-ION CONCENTRATION<sup>1</sup>

ERNEST B. HANAN AND WALTER P. ERICKS

In attempts to develop a procedure for precipitation of tuberculin-like substances from the urine of patients with active tuberculosis the authors employed the buffer solution method of hydrogen-ion concentration. Working with known solutions of tuberculo-protein, it was observed that the optimum pH concentration for maximum precipitation was approximately 2.8. This is apparently in disagreement with the results obtained by both Gabbe (1) and Long and Seibert (2). These investigators placed the isoelectric point for maximum precipitation at approximately pH 4.0.

In view of the importance of this observation in relationship to the chemistry of tuberculosis it was deemed advisable to investigate this point more thoroughly.

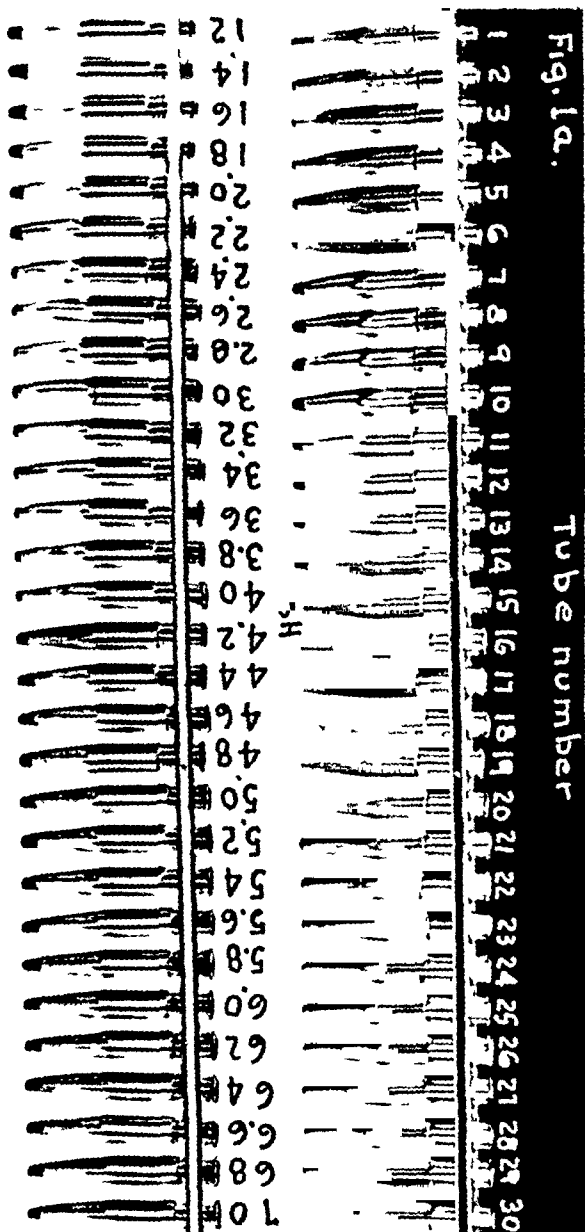
## PROCEDURE

Various buffer solutions were tried with different preparations and amounts of tuberculo-proteins. The experiments presented here were performed with the standard buffer solutions of Clark and Lubs (3). A series of 30 different pH concentrations ranging from 1.2 to 7.0 was tested. These pH concentrations were measured before and after the addition of the protein solutions by the colorimetric method and checked by the potentiometer. Care was used not to disturb the pH equilibrium of the buffer solutions by addition of too much protein extract.

The tuberculo-protein solutions tested were the ultraprotein filtrate prepared according to the method of Seibert (4), distilled water extracts of virulent and avirulent tubercle bacilli, and the undialyzed culture filtrate of avirulent tubercle bacilli grown on Long's (5) nonprotein media.

In the experiments described in this communication, the undialyzed culture filtrate was used. It was found that 0.5 cc. of the filtrate could

<sup>1</sup> From the Laboratories of the Buffalo City Hospital and Medical School, University of Buffalo, Buffalo, New York.



**Fig. 1b**

Fig. 1a. Showing the precipitation of tuberculo-protein by hydrogen ion concentration using Clark and Lubs's buffer solutions. The pH range is from 1.2 to 7.0. Optimum pH for maximum precipitation is 2.5 with a range from 2.4 to 3.0.

Fig. 1b. Showing precipitation of the tuberculo-protein from supernatant fluids of test shown in fig. 1a using 10 per cent concentration of trichloroacetic acid. Note that practically no precipitate appears at pH 2.5.



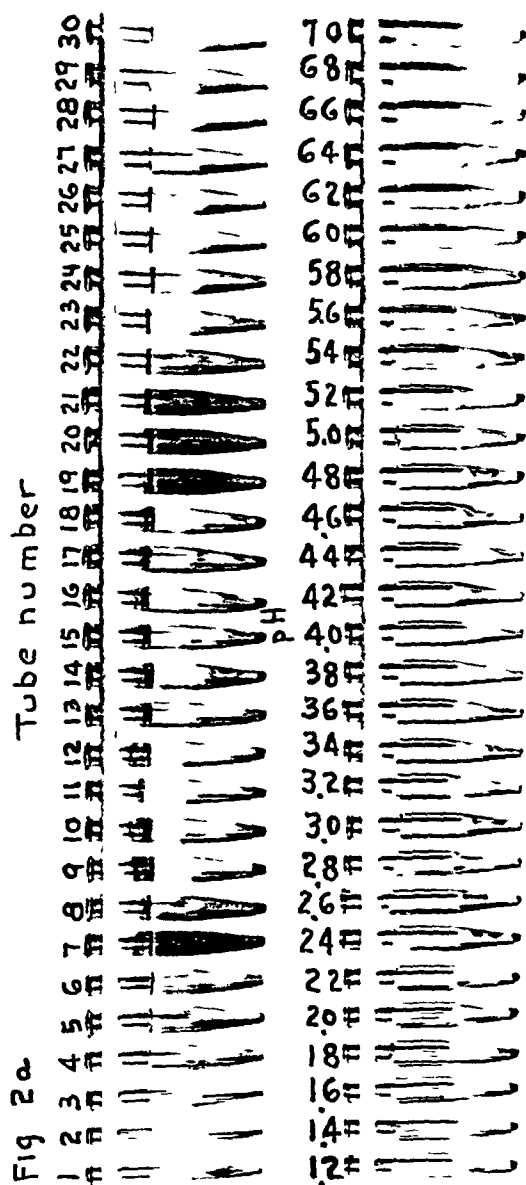


Fig. 2a. Showing pH precipitation of heated tuberculo-protein using the same technique as in fig. 1a. Note that the range of maximum precipitation shifts to the alkaline side to pH 46.

Fig. 2b. Trichloroacetic acid precipitation of supernatant fluids of experiment 2a. Note that practically no precipitate appears within the pH range of maximum precipitation.

be added to 9 cc of the buffer solutions without disturbing the pH equilibrium. Nine cc of each buffer solution was pipetted into a centrifuge tube followed by 0.5 cc of the culture filtrate. This was mixed and observed for the appearance of flocculation, then, after standing overnight, the tubes were centrifuged and observed for the pH concentration of maximum precipitation.

The supernatant fluids were then transferred to another set of tubes and tested by various protein precipitants for completeness of precipitation. In these experiments, trichloroacetic acid was added making a 10 per cent concentration, and after standing overnight the tubes were centrifuged. The completed experiment is shown in figures 1a and 1b.

Following this a culture filtrate was boiled for one hour and the experiment repeated as shown in figures 2a and 2b.

### RESULTS

In the experiments with the different tuberculo-protein solutions, it was observed that flocculation appeared first at pH 2.8. This was the finding regardless of the method of preparation of the protein solution. On standing overnight the maximum range for the unheated culture filtrate extended from pH 2.4 to 3.0 as shown in figure 1a and also tended to extend toward the alkaline side to pH 4.0 but precipitation was not complete beyond pH 3.0.

With the heated culture filtrate, the flocculation appeared first at pH 2.8 but on standing overnight the maximum range of precipitation extended toward the alkaline side to pH 4.6 as shown in figure 2a.

When trichloroacetic acid was added to the supernatant fluids as shown in figures 1b and 2b, very little precipitate occurred within the maximum range of pH precipitation.

### DISCUSSION

Our experience with the pH precipitation of tuberculo-protein has shown that with the undenatured material the optimum point for the maximum precipitation is approximately pH 2.8 with a range between 2.4 and 3.0. However, when subjected to hydrolysis as in heating, the maximum range extends towards the alkaline side to as high as pH 4.6. This was especially noted with the distilled aqueous heat extracts of tubercle bacilli.

Attempts were made to repeat the experiments of Long and Seibert,

using acetic acid. A series of 60 tubes were set up, each containing 9 cc. of a diluted aqueous extract of avirulent tubercle bacilli.

Beginning with dilute acetic acid that gave no precipitate in the first few tubes, the amount of acid was increased in each successive tube until no precipitate occurred in the last few tubes. The pH was determined colorimetrically in the supernatant fluid of each tube. It was found that the pH did not consistently vary in proportion to the amount of acid but it was interesting to note that all maximum precipitations occurred within the pH 2.4 to 4.6 range. This was the same range as obtained with the same extract using the buffer solutions.

Blood serum or egg albumen (using the same buffer solutions) does not precipitate at pH 2.8. This would indicate that tuberculo-protein is probably not albuminous in nature as has been suggested by some investigators (6) (7). At least it does not precipitate in the albumen pH range until subjected to hydrolysis. This may have caused confusion since the hydrolyzed material has probably become a mixture of derived proteins, some of them albuminous in nature.

The precipitate obtained at pH 2.8 is readily soluble in distilled water made slightly alkaline with sodium-bicarbonate. It gives positive biuret and xanthoproteic reactions and contains a carbohydrate radical as indicated by Molisch's test.

Its antigenic properties were demonstrated by the characteristic tuberculin skin reactions on tuberculin-sensitive individuals. A satisfactory antigen for complement fixation tests has been prepared in our laboratory by using a precipitate obtained by adjusting the aqueous extract of tubercle bacilli to pH 2.8 with glacial acetic acid.

There are but few proteins that precipitate at so low a pH. This suggested a chemical aid for isolation and purification of tuberculo-protein. In order to test this possibility, a mixture of tuberculo-protein and human serum in equal amounts was added to a series of buffer solutions, and allowed to stand overnight. At the lowest pH of maximum precipitation (pH 2.4) very little serum proteins were adsorbed to be carried down by the tuberculo-protein, but as the alkaline side was approached more and more serum proteins were carried down. In the pH range for precipitation of serum proteins the tuberculo-proteins were apparently adsorbed and carried down with the serum proteins.

This reaction has not been investigated further at the present time. However, we have used the pH 2.8 precipitation as an aid in the isolation

and purification of the tuberculin-like substances in the urine of patients with active tuberculosis with some degree of success

The authors feel that on further studies this low pH flocculation point may prove to have considerable bearing upon our knowledge concerning the nature of the disease processes of tuberculosis. It may also explain some of the difficulties encountered in laboratory procedures now employed as aids in diagnosis of the disease.

#### SUMMARY

1 By use of buffer solutions it was found that with undenatured tuberculo-protein the maximum precipitation occurs at approximately pH 2.8 with a range from 2.4 to 3.0

2 When tuberculo-protein is subjected to hydrolysis the range of maximum precipitation shifts toward the alkaline side to as high as pH 4.6

3 It is suggested that this low pH 2.8 precipitation point may serve as a chemical aid in the isolation and purification of the tuberculo-protein

4 It is further suggested that continued studies of pH precipitation characteristic of tuberculo-protein may have an important bearing on our knowledge concerning tuberculosis

The authors wish to express their appreciation to Alexander Terech and William Miller-schoen for their invaluable technical assistance rendered in these studies

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# TOPICAL APPLICATION OF CODLIVER OIL IN TUBERCULOSIS<sup>1</sup>

A Preliminary Report

ANDREW L. BANYAI

The administration of codliver oil by mouth was known for a long time before experimental evidence was produced that demonstrated its possible mode of action. In the earliest references its alleged usefulness was attributed to its relatively easy absorbability from the intestinal tract and to its high caloric value.

When it became known that codliver oil contains large amounts of vitamin A and vitamin D, it was demonstrated that certain healing properties of it were due to these vitamins.

The results observed by Loehr (1) following the local application of codliver oil in nontuberculous conditions are of interest. He used codliver oil and a codliver-oil salve for the treatment of fresh wounds, burns, acute and chronic osteomyelitis. He noted that codliver oil exerts a striking inhibiting effect upon the bacterial flora of wounds. The oil permeates the tissues and causes a rapid liquefaction of the necrotic tissues, including the epithelium. There is an early appearance of granulation tissue which, in turn, becomes covered with epithelium. The most striking regenerative effect on the epithelium was seen in burns.

The favorable effect of codliver oil upon the formation of granulation tissue was observed by Steel (2) in the treatment of deep abrasions, burns, and indolent ulcers in the leg.

Loehr (1) emphasizes the fact that bacteria ordinarily encountered in infected wounds, such as streptococci, staphylococci and *Bacillus coli*, perish when introduced into codliver oil. It has not been determined whether the microorganisms die because the codliver oil contains no nourishment for them or because of the surface tension of the oil. He believes that the beneficial effect of codliver oil upon the healing of wounds is attributable to its vitamin A and D content.

<sup>1</sup> From the Muirdale Sanatorium, Wauwatosa, Wisconsin.

Fontes (3) reported in 1921 that the addition of one per cent codliver oil to ordinary broth medium prevents the development of cultures of tubercle bacilli. The oil in the fluid medium did not lose this inhibiting power when filtered through porcelain but did lose it when shaken with kaolin. Fontes assumed that the bacilli absorb particles of oil which forms an insulating envelope that, in turn, obstructs the nutrition and oxygen supply of the microorganisms.

The inhibitory effect of codliver oil upon the growth of tubercle bacilli was believed by Platonov (4) to be due to unsaturated fatty acids. He added the unsaturated soaps of codliver oil to cultures of tubercle bacilli on potato media. After three weeks it was found that unsaturated soaps, even in concentration of 0.25 per cent, inhibit the growth of the bacilli. When suspension of tubercle bacilli in a one or two per cent solution of unsaturated soaps was used, the effect was still greater. After 48 hours in the incubator, the preparation stained by the Ziehl-Neelsen method had an interesting appearance: the tubercle bacilli were pale pink, contained dark granules and a considerable number of them had lost their acid-fastness.

A similar investigation was carried out by Campbell and Kiefer (5). They cultured tubercle bacilli on codliver-oil-potato medium. After five weeks the tubercle bacilli appeared beaded and smaller than the usual size. Some of them had a dumb-bell shape and seemed to be composed of two granules united by a very thin short strand of red-staining protoplasm. With the granule stain, the red-staining protoplasm was not very evident. Many solitary granules were seen. They concluded from their investigation that codliver oil has a definite inhibitory and bactericidal action on virulent tubercle bacilli. From the study of controls on cotton-seed oil they deduced that at least part of the inhibitory action is caused by some constituent of the codliver oil and not altogether by a mechanical action of a film of oil between the bacterium and the medium.

Loehr (1) also reported that codliver oil is free of bacteria and, even when used in large quantities locally, it is harmless.

This paper is based upon the observation of 46 cases. Of these there were 3 lupus vulgaris, 1 scrofuloderma, 1 case with multiple subcutaneous tuberculous abscesses, 6 with tuberculous lymphadenitis, 1 so-called primary tuberculosis of the muscle, 2 tuberculous ulcers of the pharynx, 25 with tuberculous laryngitis, 3 with tuberculous empyema, 1 sinus following tuberculous epididymitis, and 3 ischiorectal fistula.

cases Patients whose treatment lasted for less than two months were not included in this study

Of the 3 lupus vulgaris cases, 2 completely recovered in eight and four months, respectively, the third patient whose lesion involved the middle and upper portions of the left arm has shown remarkable improvement during the five months from the beginning of treatment on March 2, 1936 This patient, N Z (no 8348), 33 years old, white, female, has been suffering from skin tuberculosis for approximately twenty years Although the lesion showed considerable improvement on a modified "salt-free" diet, rather large, persistently discharging ulcerous areas were still present at the beginning of codliver-oil treatment As an illustration of complete healing the following case is presented

O K, (no 6814), 27 years old, white, female Diagnosis Lupus vulgaris, involving practically the entire face, with partial destruction of the nose and upper lip Also, lupus vulgaris, involving the entire extent of the skin of the left arm The disease was of 6 years' duration when patient was first seen The process responded favorably to "salt-free" diet, but some of the ulcers on the face and arm remained open and produced considerable discharge Codliver-oil dressings were applied to these areas from October 4, 1934 until May 31, 1935, at which time all ulcers were found to be epithelized The favorable change in the process of healing was so marked following the local application of codliver oil, that it seems to be justified to attribute the acceleration and completion of the healing to the effect of codliver oil

Favorable response to treatment is present in a case of scrofuloderma following a period of treatment of  $4\frac{1}{2}$  months The process is not entirely healed yet The lesion in this patient, M C (no 7856), 13 years old, Mexican, male, developed at the site of multiple sinuses originating from tuberculosis of the right 6th rib

Slow but satisfactory improvement followed the application of codliver oil to ruptured tuberculous subcutaneous abscesses This child, W F (no 9384), 15 years old, colored boy, was suffering also from multiple bone tuberculosis and tuberculous lymphadenitis

Very good results were observed in all the six cases of tuberculous adenitis Two cases are presented in detail

I A B, (no 10197), 2 years old, white, female Diagnosis tuberculous lymphadenitis, preauricular On admission there was a fluctuating mass the size of a large walnut anterior to and below the right ear The skin over

this abscess was markedly congested and atrophic. The patient was treated by dark quartz-lamp irradiations at the Milwaukee Children's Hospital prior to her registration at the sanatorium, without improvement. Fifteen cc of pus were removed from the abscess by aspiration, following which 5 cc of warm codliver oil were injected into the abscess on April 4, 1936. The abscess broke through the skin two days later. Next day it closed up again and began to fill up. Four cc of pus were aspirated and 2 cc of warm codliver oil injected on April 11, 1936. The abscess opened spontaneously the same night. From then on the local treatment consisted of daily instillations of codliver oil by means of medicine dropper and of the application of codliver-oil dressings over the discharging sinus. The discharge gradually diminished and complete healing ensued in three months.

The development of a small fluctuating abscess, originating from a tuberculous lymphadenitis was noted under the chin on April 25, 1936. Aspiration was unsuccessful. When this abscess opened spontaneously, codliver-oil dressings were applied locally. On July 25, 1936 there were two small sinuses under the chin. The drainage from them was only occasional and scanty. Codliver-oil dressings were substituted by the topical application of an ointment that consists of equal parts of codliver oil and vaselin.

2 M P, (no 10079), 15 years old, white, male. Diagnosis bilateral tuberculous inguinal adenitis. Two months prior to his admission to the sanatorium he noticed a progressive swelling in both inguinal areas, about the size of small eggs. Two weeks later both swellings were surgically evacuated at the Milwaukee County General Hospital. The diagnosis of tuberculosis was confirmed by a postoperative biopsy. Both wounds measured about 9 cm in length and had a profuse, purulent discharge when first seen. Codliver-oil packs were applied twice daily. Three weeks after the beginning of this treatment a walnut-sized swelling developed above the left incision. It disappeared in about a week without surgical intervention. After six weeks' treatment with codliver oil the right wound was completely filled with granulation tissue and was partly covered with new epithelium, the healing of the left side was somewhat slower, but the granulation and epithelization were progressing satisfactorily. No other local measures were applied. The patient gained 8.5 kgm (19 lbs) in seven weeks and 12.5 kgm (27.5 lbs) in 8 months. Complete healing occurred in 8 months.

The case of a so-called primary tuberculosis of the muscle is presented briefly.

R W, (no 9570), 40 years old, white, male. Diagnosis (1) Far-advanced pulmonary tuberculosis, (2) so-called primary tuberculosis of the muscle,



left forearm The tuberculous mass was removed surgically by Dr F Raine on October 12, 1935 Because of the persistent drainage following this operation, codliver-oil packings were applied daily from November 29, 1935 There was a rapid diminution in the amount of discharge shortly after beginning of this treatment The wound healed completely and was well epithelized in six weeks

The rapidity with which tuberculous pharyngeal lesions cleared up was surprising The following case illustrates this point

L L, (no 10103), 20 years old, white, female Diagnosis (1) Far-advanced pulmonary tuberculosis, (2) tuberculosis of the tonsils and peritonsillar structures, (3) tuberculous laryngitis The patient stated that her throat condition developed two months before her admission to the sanatorium She complained of sore throat and dysphagia Both anterior and posterior pillars and both tonsils were markedly congested, the right tonsil and the right anterior pillar were definitely ulcerated The same involvement was present on the left side, although not very extensive There was considerable anterior cervical adenopathy The throat was cleansed with Dobell's solution, and codliver-oil spray was applied locally three times a day In three weeks the ulcers disappeared, the margins of the pillars were smooth, and congestion of these structures entirely cleared, except the posterior part of the right tonsillar fossa, the latter was found normal 4 weeks later The soreness of the throat and dysphagia disappeared

It is interesting to note that her larynx has shown a healing of the tuberculous ulcers but the oedema persisted, although it was treated with codliver oil during the same period

All patients in the laryngeal tuberculosis group had an active pulmonary tuberculosis Some had also other extrapulmonary complications As to the pathology, a great many manifestations of the disease were seen, from a well circumscribed infiltration to ulceration, marked interarytenoid vegetative granulation, and extensive oedema

The treatment of the larynx consisted of spraying it with codliver oil by means of an atomizer three times a day The spray was given always after meals for avoiding possible anorexia caused by the taste of the oil The oil must be warmed prior to its application, for two reasons (1) heating diminishes its viscosity, and (2) the diseased mucous membrane tolerates warm oil better than cold oil The patient is instructed to hold the tongue between the thumb and the index

finger Pulling the tongue forward with moderate force causes a rise of the larynx and thereby facilitates the proper focusing of the spray The nurse or attendant, instructed in the technique, holds the downward directed tip of the atomizer slightly beyond the root of the tongue, without touching the pharyngeal structures The patient breathes in and out somewhat faster than usual, 10 to 12 compressions of the bulb of the atomizer deliver a sufficient amount of oil into the accessible parts of the larynx

The length of treatment varied from 2 to 6½ months

The evaluation of the effect of codliver oil in laryngeal tuberculosis is rather difficult for several reasons Tuberculous laryngitis may show a spontaneous healing in its early stages Its course may parallel that of the pulmonary process When the general condition of the patient, his immunity and defense are poor the chances for improvement in a serious laryngeal tuberculosis are very slight

Still it seems that, perhaps, with the exception of cases with marked laryngeal oedema, or when the pulmonary tuberculosis is very advanced, it is worth while to resort to codliver-oil treatment The restoration of normal voice, the elimination of dysphagia, the relief from soreness in the larynx and from exhausting cough, improved expectoration, and restoration of normal sleep, that accompanied objective evidence of improvement in some of our cases, speak very much in favor of such an attitude

Of the 25 patients in this group, 17 improved and 8 did not Of the 8 patients who showed no improvement 6 had far-advanced pulmonary tuberculosis Some of them have serious complications, such as, diabetes, empyema, and renal tuberculosis Marked laryngeal oedema was present in four This type of lesion is particularly resistant to local treatment Of the 17 patients who improved, 9 had far-advanced pulmonary processes

Three cases of tuberculous empyema were treated The treatment consisted of the injections of 45 to 300 cc of codliver oil into the thoracic cavity through a catheter that had been inserted previously None of these patients showed a satisfactory improvement on surgical drainage following costectomy The treatment was well tolerated by the patients No local or general reactions resulting from the treatment were observed One patient, R W, (no 9658), white, male, who had a progressive pulmonary tuberculosis on the "good" side, died The

treatments were given for 2½ months. A slow but definite improvement has been noticed in the second case, N S, (no 9757), 34 years old, white, male. The details of the course of treatment in the third case were as follows:

S J, (no 4192), 37 years old, colored, male, was discharged from the sanatorium as an apparently arrested case of far-advanced pulmonary tuberculosis on October 22, 1934. At the time of his readmission, July 2, 1935, he complained of loss of weight and strength, and stated that he noticed a swelling over the right breast region. The right thoracic cavity was aspirated on several occasions and pus removed. An *empyema necessitatis* developed on July 23, 1935. There was a persistent purulent drainage through the sinus. The temperature that rose over 39°C shortly after his admission, returned to normal in four months, with occasional subfebrile rises. A costectomy was performed and drainage established on November 14, 1935.

Because of the persistent drainage and because of the lack of improvement in the patient's general condition we resorted to the injection of about 150 cc of codliver oil into the empyema cavity on February 25, 1936. Following the injection the drainage tube was clamped near the chest wall, and the clamp was left in place from half an hour to two hours, then drainage was established through a tube, the distal end of which was connected to an ordinary drainage bottle. The oil was warmed to body temperature prior to the injection. These treatments have been repeated once a day. No pleural reaction, pain, discomfort or cough followed the injections. The amount of purulent discharge became gradually less, and it was found to be thinner and more watery than before as the treatment progressed.

The patient is in a greatly improved general condition. He gained 13.5 kgm (29.7 lbs) in weight in 5 months, since the beginning of the codliver-oil treatment.

A gradual improvement has been observed in a patient with a tuberculous fistula following an operation for tuberculous epididymitis. The duration of treatment is six months. Recently, because of the shallowness of the sinus tract, the codliver oil, that was applied by means of a medicine dropper directly into the sinus previously, was substituted by a 50 per cent codliver-oil ointment.

Patients with ischio-rectal fistulae were given daily injections into the fistula after cleansing it with physiological saline solution. Warm oil is more likely to penetrate the fistulous tract than cold oil. There was marked improvement in 2 and complete healing in 1 patient. In the latter case recovery occurred in 5 months.

J K, (no 6494), 33 years old, white, male Diagnosis (1) Far-advanced pulmonary tuberculosis, (2) tuberculous laryngitis, (3) tuberculous ischio-rectal fistula The rectal fistula was of three years' duration when local treatments were started with daily injections of codliver oil After six weeks' treatment the pain, that prior to treatment was radiating upward along the spine, became less marked, the amount of discharge markedly diminished, and the sinus tract, that previously admitted the tip of a rather large syringe, was so well filled with granulation that only a medicine dropper could be used for injecting the oil Complete healing in 5 months

W C, (no 8920), 19 years old, white, male Diagnosis Active far-advanced pulmonary tuberculosis Complications (1) Tuberculous laryngitis, (2) tuberculous ischio-rectal fistula A draining ischio-rectal fistula was noted on August 11, 1935 A second fistula developed on November 11, 1935 Treatment with codliver-oil injections into the fistulous tracts began on December 15, 1935 The injections were given with the patient in the prone position He was kept in this position for 20 minutes after each injection The treatments have been repeated daily The patient reported subjective improvement in the rectal condition on January 9, 1936 On periodic examinations it was found that the amount of discharge was decreasing The amount of codliver oil that we were able to inject was getting less also On April 30, 1936 the lower fistulous tract was found to be noticeably decreased in depth, its cutaneous opening showed a clean granulation tissue, and only a shallow crater remained from the deep tract The lateral sinus healed entirely The patient's general and pulmonary condition remain stationary

#### SUMMARY

Because of the limited number of cases, no attempt is made to draw definite conclusions It may be stated, however, that codliver oil can be applied topically with safety in tuberculous laryngitis and pharyngitis, ischio-rectal fistulae, lupus vulgaris, suppurating tuberculous lymphadenitis, tuberculous empyema, and other forms of tuberculosis described above

The favorable results seen in certain types of tuberculosis in our cases invite further study of the therapeutic value of the topical application of codliver oil

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# PARACARDIAC PULMONARY EMPHYSEMA<sup>1</sup>

## A Heretofore Undescribed X-ray Shadow Complex

EPHRAIM KOROL<sup>2</sup>

In many chest roentgenograms a group of curvilinear shadows is seen running parallel to the left border of the heart, about one centimetre outside of it. The space between this crescent-shaped density and the heart is very transparent, producing a halo effect about the left border of the heart. The halo may be followed through the shadow of the dome of the diaphragm to the lower border of the lung (figure 1). Upon closer inspection this bright area is seen to be crossed by several fine curved lines which outline circular and oval areas of transparent lung. In many cases a similar region of transparent lung with a dense outer border is seen to the left of the descending aortic arch. Less often the lung in the vicinity of the right border of the heart shows similar changes. Upon stereoscopic examination it can be seen that the lung changes are situated in the front of the chest near the anterior chest wall, while bronchographic examination shows that the shadows are not related to the bronchial trunks (figures 4a and 4b).

The transparent lung areas become more conspicuous on films taken in expiration, the transparencies are accentuated in contrast with the opacification of the lung bases occurring in expiration. Apparently we are dealing with lung tissue which does not deflate well during expiration, that is, with emphysematous lung.

We have had the opportunity to follow three cases with these paracardiac lung changes to postmortem examination, in all cases there was pronounced emphysema in the left upper lobe, chiefly involving the lingula, and there were no other changes such as bronchiectasis, tuberculosis, etc., to account for the roentgen shadow complex.

The paracardiac emphysema when developed sufficiently to show on the X-ray film is generally associated with an enlarged heart. In its most pronounced degree it occurs in cases of aortic regurgitation. We

<sup>1</sup> Published with the permission of the Medical Director of the Veterans Administration, who is not responsible for opinions expressed or conclusions drawn by the author.

<sup>2</sup> Veterans Administration Facility, Lincoln, Nebraska.

have not observed this shadow complex in cases of small centrally-placed hearts. In these cases the descending vascular trunks come to show outside of the heart shadow, but the transparent area of lung tissue described above does not appear in these cases.

It should be emphasized that this shadow complex is not evidence of generalized emphysema. In fact it is seldom seen in severe bullous emphysema and in the forms of obstructive emphysema associated with asthma and chronic bronchitis. Rather, the shadow complex is an expression of emphysematous changes affecting the lobules immediately adjacent to the heart and aorta. The causes of this emphysema reside in the traumatizing action which the pulsating heart has on the surrounding lung.

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Fig 1 Aortic regurgitation of twenty years' duration. The heart action was very forcible and fluoroscopically there was striking overactivity of the left ventricle and of the aorta. The pulse pressure was 120 systolic 160, diastolic 40 mm Hg. The base of the left lung is more transparent than the right and the diaphragm is depressed on this side. Outside of the heart border there is the typical crescent of paracardiac emphysema. A similar band of emphysema borders the descending aorta.

Fig 2 Case of hypertensive heart disease. Blood pressure 200/120 mm Hg. The apex impulse was heaving in character and there was a cardiorespiratory murmur. The left base is emphysematous, the transparent lung overlapping the heart apex and the dome of the diaphragm. Note the crescents of paracardiac and preaortic emphysema.

Fig 3 Double mitral lesion of many years' duration. The crescent of paracardiac emphysema is well marked. In this figure the border of the emphysema crescent is fortified with pencil marks.

Fig 4a Case of hyperthyroidism. Increased rate and force of heart. Blood pressure 150/80 mm Hg. Cardiorespiratory murmur. Note the ribbon of paracardiac emphysema parallel to the left heart border.

Fig 4b Same case as in fig 4a. Lipiodol in the descending bronchi, to show that they are not concerned in the shadow complex of paracardiac emphysema.

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*Physiological Considerations* Pulmonary emphysema is a very common condition, it occurs in the majority, perhaps in all adults coming to autopsy. In its earlier stages it is confined to the anterior margins of the upper lobes, the left lung being affected earlier and more extensively than the right. Elsewhere (1) we discussed in detail the preference of emphysema for the paracardiac lung regions. The contractions of the heart exert a ventilatory action on the lung: during systole the neighboring lung lobules expand, the succeeding diastolic dilation of the heart collapses these lobules. This respiratory activity of the heart is increased in cardiac hypertrophy, particularly in cases

Fig 1



Fig 2

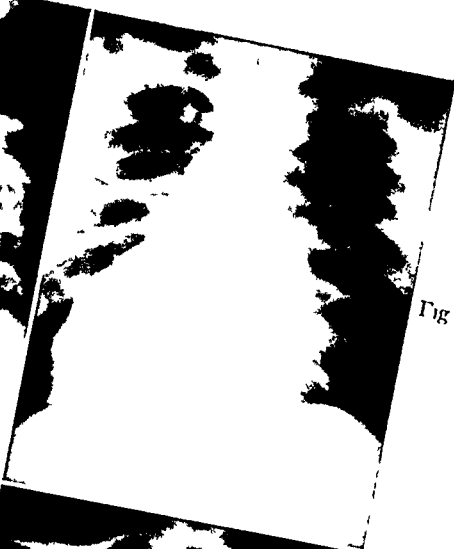


Fig 3



Fig 4a



Fig 4b





of aortic and mitral valve insufficiency, also in the cases of tachycardia and functional hyperactivity of the heart. In these conditions the paracardiac lung regions may be actuated by the heart contractions quite as much or more than by the respiratory muscles. The left upper lobe comes to be the most exercised lung region, and is for this reason the commonest site of emphysema.

The paracardiac emphysema usually produces no symptoms and no marked X-ray changes. Only when unduly developed, generally in association with hypertrophy of the left heart, are the lung changes extensive enough to produce the shadow complex described above.

#### SUMMARY

In the base of the left lung, parallel to the heart border, there is often observed a sickle-shaped area of increased transparency with a well defined outer border. After several postmortem observations and a study of the cardiorespiratory dynamics, this shadow complex is identified as an expression of emphysema involving the lobules bordering the heart.

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## THE RELATION OF INTRAPLEURAL PRESSURES TO THE FORMATION OF EFFUSIONS IN ARTIFICIAL PNEUMOTHORAX<sup>1</sup>

LUCIUS N TODD<sup>2</sup>

The impression that positive intrapleural pressures are conducive to the formation of effusions in artificial pneumothorax is rather widespread among tuberculosis specialists. It is voiced in the literature and can be heard in almost any discussion of the subject.

In an admittedly incomplete review of the literature, we encountered this impression frequently, but were unable to find much in the way of statistical data to substantiate it. Fishberg (1) feels that effusions are less likely to occur in complete than in partial collapse. He also is of the opinion that the longer pneumothorax lasts, the more certain effusion is to appear.

In contradistinction to this is the statement of Bunta (2) that the largest percentage of effusions appear in association with the largest pneumothorax cavities, 43 per cent of the patients with X-ray evidence of fluid in his series also showing complete or almost complete collapse. In another study he (3) presents some interesting figures, comparing the degree of collapse with the percentage of effusions, and finds that 6 per cent of patients with 5 to 25 per cent collapse had fluid and pressures ranging from minus 10 to plus 6. In patients with 80 to 100 per cent collapse, 59 per cent had fluid and pressures ranged from plus 3 to plus 9. These figures indicated to Bunta that fluid varies directly with pressure. In his series of 860 cases receiving artificial pneumothorax, only 183, or 21.3 per cent, ever showed any evidence of fluid. This is attributed in part at least to negative intrapleural pressures.

Van Horne (4) found fluid more frequently in positive-pressure cases. This he thinks is due, not so much to the pressures, as to the fact that there is a larger pleural space. He strongly favors positive pressures, however, when necessary to obtain satisfactory collapse.

<sup>1</sup> Read before the Southern Tuberculosis Conference and Sanatorium Association, Hot Springs, Arkansas, October 1-3, 1936.

<sup>2</sup> Waverley Hills Sanatorium, Waverley Hills, Kentucky.

Graham, Singer and Ballon (5) state that the reason they have encountered so few effusions is because they always employ small refills and remain on the negative side of intrapleural pressure

Riviere (6) urges the lowest pressure sufficient to maintain satisfactory collapse, but does not hesitate to employ positive pressures when indicated. He states also that it has been demonstrated that high positive pressures as a rule fall rapidly during the first few hours after a filling

In an effort to throw some light on this controversial subject we have made a careful study of the records of 215 patients receiving artificial pneumothorax at the Waverley Hills Sanatorium. The majority of these patients have been discharged, and they return to our Outpatient Department for treatment. This group was selected for study because of the length of time they have been receiving treatment, some of them as long as ten years. In addition to these patients, we checked the records of cases still in the Sanatorium, and included all those having fluid and all those having positive pressures, whether they had fluid or not. No case was considered that had been receiving treatments less than six months. Our patients are routinely X-rayed every four to six months while in the Sanatorium and every six months in the Outpatient Department. In addition, they are fluoroscoped at each refill. In our study we not only checked the pneumothorax record with the X-ray, but, to obtain all possible information, we quizzed each patient as to whether or not they had any knowledge as to the presence of fluid at any time. It is surprising to find how closely patients follow their own progress, and we were able to check the record in some questionable instances very satisfactorily with their aid.

In any discussion of intrapleural pressures, it is well to remember that many factors enter into the determination of what is really the true pressure in any given case. Patients with a flexible mediastinum or with hernia will not register pressures under all conditions that will be comparable to those having a fixed mediastinum or paralyzed diaphragm. Posture also has a marked influence on intrapleural pressure, as can be easily demonstrated by introducing a needle into the pleural space and connecting the manometer. Have the patient roll over from one side to the other. A marked elevation will be noted when lying on the pneumothorax side. All of us who are accustomed to administer refills with the manometer open have had the experience of having the patient

cough unexpectedly and force the water out of the tube, showing a high, even if temporary, pressure. It is easy to visualize what happens in

TABLE 1

Total number of patients	215	<i>per cent</i>		100
Number of women	134			62
Number of men	81			38
Number of patients without fluid	86			40
Number of patients with fluid	129			60
	Without fluid		With fluid	
		<i>per cent</i>		<i>per cent</i>
Patients with negative pressure	27	31	64	50
Patients with zero pressure	3	4	10	8
Patients with positive pressure	56	65	55	42

TABLE 2

INTRAPLEURAL PRESSURES	WOMEN									MEN										
	Under 25 years					Over 25 years				Under 25 years				Over 25 years						
	M A		F A			M A		F A		Total	M A		F A		M A		F A		Total	Grand total
	Right	Left	Right	Left	Right	Left	Right	Left	Right		Left	Right	Left	Right	Left	Right	Left			
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left		
Without fluid																				
Negative	6	2	3	2	1	0	1	1	16	2	2	0	0	1	2	3	1	11	27	31
Zero	0	0	0	0	1	1	0	1	3	0	0	0	0	0	0	0	0	0	3	4
Low plus	0	1	1	0	2	2	1	0	7	0	0	0	1	0	1	2	1	5	12	14
Moderate plus	3	2	1	4	1	4	1	5	21	0	0	0	4	2	0	1	2	9	30	35
High plus	1	2	1	1	1	1	2	1	10	0	0	2	1	0	0	0	1	4	14	16
With fluid																				
Negative	6	7	6	6	4	4	5	4	42	2	3	1	1	3	1	4	7	22	64	50
Zero	0	0	1	0	0	1	0	2	4	0	0	0	1	1	0	2	2	6	10	8
Low plus	0	0	0	3	0	3	0	0	6	0	1	2	1	1	2	1	4	12	18	14
Moderate plus	1	1	1	2	0	0	4	6	15	1	0	1	1	2	0	2	0	7	22	17
High plus	2	1	0	2	0	1	2	2	10	0	0	0	3	0	0	2	0	5	15	11
Total	19	16	14	20	10	17	16	22		5	6	6	13	10	6	17	18		215	

Note Low plus = Under plus two, Moderate plus = Under plus eight, High plus = Over plus eight Corrected manometric readings

patients even with negative pressures who do an excessive amount of coughing

In presenting this study, we wish to make it clear that we do not intend to convey the impression that we have recorded every effusion, however slight, which occurred in these patients. Not an inconsiderable number of cases will show a small collection of fluid in the costophrenic sulcus, which is evanescent and possibly is only observed at a single fluoroscopy. We do feel, however, that we have not overlooked effusions that were enough to alter pressures or remained present for at least a month.

Table 1 epitomizes the results of our investigation. It will be seen that 35 per cent of the patients without fluid had zero or negative mean pressures as compared to 58 per cent of those with fluid, leaving 65 per cent without fluid showing positive pressures as against 42 per cent in the fluid group.

Table 2 gives a detailed analysis of the figures, dividing the patients according to sex, age, stage, side and pressure. The subdivision of the positive-pressure cases was purely arbitrary but gives considerable aid in evaluating the results. Quite a few of the patients in the high-pressure group had pressures too high to be measured by the water manometer. Of this group, 16 per cent without fluid had high positive pressures as against 11 per cent with fluid.

#### CONCLUSIONS

A study of 215 cases of artificial pneumothorax has been presented and a comparison made between those having effusions and those having none.

We feel that we are justified in concluding that positive intrapleural pressures are not conducive to the formation of effusions, and personally we never hesitate to employ them when indicated.

This study strengthens the impression that we must look elsewhere for the principal causative factors in the production of effusions and we are in agreement with our associates (7) on this point.

It is our intention to present statistical data upon other mechanical factors which might possibly play a part in the formation of effusions in a future study.

We wish to express our appreciation to Miss Rena Washburn, R N, for invaluable aid in the correlation of the statistical data.

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# TRANSTHORACIC TREATMENT OF TUBERCULOUS CAVITIES<sup>1</sup>

A Preliminary Report

M JACOBS AND H M BELOFF

The cavity in tuberculosis of the lungs is a focal point upon whose adequate treatment hinges, to a great extent, the fate of the patient. The existence of excavation is a large factor in the determination of the applicability and type of surgical therapy, and there is no more important gauge of the efficiency of treatment in pulmonary tuberculosis than the progress or regression of cavities. This acknowledged importance of cavities in relation to the pathological course, clinical prognosis, and the success of the collapse therapy in pulmonary tuberculosis, is mentioned because the procedure we are describing has for its purpose the direct treatment of cavities.

The local attack of a tuberculous cavity without recourse to surgical interference is not new. Old tuberculous cavities have been treated by the laryngeal route with metaphen-in-oil (Jacobs (1)) and in the last few years the bronchoscopists have occasionally succeeded in closing cavities by producing a stenosis of the terminal end of the bronchus communicating with a cavity. By their method the tissues around the cavity became atelectatic and ultimately the cavities were closed. However, the procedure we are about to describe differs from the methods mentioned above.

In our method we attempt to attack the cavity directly through the chest wall, injecting colloidal copper morrhuate into it. Ameuille and Durbois (2) of France in 1930, MacDowell (3) (4) of Brazil were the pioneers in attempting transthoracic injections of tuberculous cavities.

The precise mode of action of the copper morrhuate, while not altogether determined, appears to depend in its greatest degree on the stenosis of the bronchus draining the cavity. There is a chemical pneumonitis set up in the pericavernous parenchyma which may play

<sup>1</sup> From the Eagleville Sanatorium, Eagleville, Pennsylvania.

some part in the healing process, as may also the constitutional effect of the copper, a heavy metal, when absorbed into the blood-stream

#### INDICATIONS

Transthoracic injection is not the procedure of choice in the eradication of any previously untreated cavity. It is admittedly a method to be used when other treatments have failed.

The cavity must be easily accessible. Most easily reached are those cavities adherent to the chest wall. In the three cases to be reported, the cavities were adherent to the anterior chest wall in the upper lobe in two cases, and to the posterior wall in the lower lobe in the third case. Close examination of chest roentgenograms taken from several angles may be necessary in order to determine whether the anatomy of the cavity is such as to be within reach of a 3-inch needle. Roentgenograms taken with the patient in the anticipated operative posture help localize the site of penetration of the chest wall.

The cases best suitable are solitary large cavities. Where there is multiple cavitation or honeycombing of a lobe with small cavities, the injection of the drug into any one such lesion will not help.

Chronic cavities, surrounded by relatively clear parenchyma, are more ideally suitable for injection than recent cavities, especially where, in the latter case, the adjacent parenchyma is the site of bronchopneumonic tuberculosis. A thin capsule of the cavity is more easily dealt with than a heavy thick one. Where the diagnosis is possible roentgenologically and from the clinical evidence (sputum analysis, presence of elastic fibres, caseous particles, highly positive sputum of considerable volume), a cavity with a fibrous wall would appear a safer type of lesion for injection than one with a necrotic caseous wall.

#### CONTRAINDICATIONS

As previously stated, the existence of multiple scattered tuberculous cavities contraindicates the injection of a single cavity.

Where there is a heavy infiltrate of pneumonic type about the cavity, so that it will be necessary to traumatize such an area by the needle during the operation, we feel that the dangers are multiplied and the procedure should not be attempted. In needling the cavity, the first trial is not always successful, and successive needle thrusts through an area of pneumonic infiltration presents the danger of carrying the infection into previously uninvolved tissues, and even introducing a notable number of organisms into the blood-stream.



## METHOD

Our cases were done with the patient lying horizontally on the fluoroscope table. The roentgenologist fluoroscopes the patient and notes on the skin the position at which the puncture should be made and the direction to be taken by the needle. The skin about the site is prepared with antiseptic solution (iodine and alcohol are used by us), and the area draped so as to give a field as sterile as possible.

The skin is then anaesthetized with 1 per cent novocaine. The operator has been prepared and gowned as for any operation where sterility is essential. A spinal needle is used for the puncture. This is attached to a 10 cc syringe carrying novocaine, and the needle is pushed through the skin, thoracic wall musculature and pleura, the novocaine being injected as the needle is advanced. When it is judged the needle has traversed the pleura, traction instead of pressure is made on the piston of the syringe, so that, if the needle enters the gas-filled cavity, it will be recognizable by withdrawal of gas into the syringe.

When it appears certain that the needle has entered the cavity, by entrance of gas into the syringe and by a sudden diminution in resistance to further progress of the needle, the syringe is removed, the trocar of the spinal needle replaced, the operative area covered by a sterile towel, and the patient again fluoroscoped to make sure that the point of the needle has entered the cavity. If this has not occurred, the direction in which the error lies is noted, and the needle withdrawn until the point is within the tissues of the thoracic wall, and the new direction taken. This procedure by trial and error, checked by fluoroscope, is carried out until the needle point unquestionably is lodged within the cavity.

The first dose of colloidal copper morrhuate that we have used is 2 cc, injected through the needle into the cavity. Subsequent injections are from 10 to 20 cc, the increase depending on whether the preceding dose was well tolerated. Injections are made at weekly intervals, and the series of injections we have used total six.

When the drug is introduced, it frequently causes a mild paroxysm of coughing, and small quantities of the drug are then expectorated, causing a characteristic taste in the mouth which our patients have described as similar to that of codliver oil.

Following the injection of the drug, the patient is immediately placed in the head-elevated position on the movable fluoroscope and kept there for ten minutes, then sent back to bed.

## REACTIONS

In approximately twenty injections which were made through the thoracic parietes, we have only one notable reaction. One patient developed a temperature that fluctuated between 100° and 102°F, beginning 24 hours after the cavity had been injected, extending over a period of four days, after which the temperature remained normal. During this febrile period the cough and expectoration were increased, but these symptoms subsided coincidently with the fall in temperature. After this period had been passed, the patient was examined fluoroscopically and no alteration in the pathology was noted. Our diagnosis was a nonspecific pneumonitis, perhaps chemical in nature, rapidly transient in its course.

## CASE REPORTS

A D 'A, white, male, 27 years old, admitted June 9, 1935, with cough, expectoration and intermittent haemoptysis of six years duration. Sputum on admission was positive (Gaffky IX), its volume in 24 hours was 130 cc. *X-ray on admission* (figure 1) *Right* The upper lobe is practically completely excavated, as is also the lower lobe. The rest is atelectatic and cirrhotic, and the entire pleura on the right side is very thick. The mediastinal structures and heart are markedly deviated to the right. The cavities are patent, made up of thick, fibrogranular walls, and quite well drained. *Left* There is a minimal fibroproliferative tuberculous infiltration in the superior retrohilar portion of the upper lobe, with a "spill-over" bronchitis in the left lower lobe behind the heart. There is a minimal nonulcerative tuberculosis of the larynx. The temperature was elevated and of a hectic type, varying from 97.6°F to 100.2°F each day, with occasional exacerbations of temperatures of 101° and 102°F.

The patient was placed on strict bed-rest, and collapse therapy considered but ruled out because of the notable dyspnoea on slight exertion. The patient remained practically in this same state of severe toxicity to December, 1935. The sputum during these months was highly positive and the volume in 24 hours varied from 105 cc to 140 cc.

In December, 1935, the injection of the cavity in the right upper lobe was begun, the patient receiving four injections of colloidal copper morrhuate transthoracically, at weekly intervals, under fluoroscopic control. The first injection was 10 cc, the others 20 cc, a total of four injections being given. The following changes have been noted in the patient since this therapy was administered: (1) The 24-hour volume of sputum is now less than half of that previously expectorated. The cough is proportionally reduced. (2) The temperature is less hectic than previously, rising no higher than 99°F.

at any time, and during many days the temperature is altogether normal  
 (3) The patient is subjectively better The sputum remains heavily positive  
 The roentgen appearance of the chest is not markedly altered except for increased density and cirrhosis in the already heavily fibrotic pericavernous tissues of the right lung (figure II)

### *Comment*

This case was chosen, not because it fulfilled our ideal indications for this form of therapy, but because we desired some easily accessible cavity upon which to standardize our technique We feel that this patient

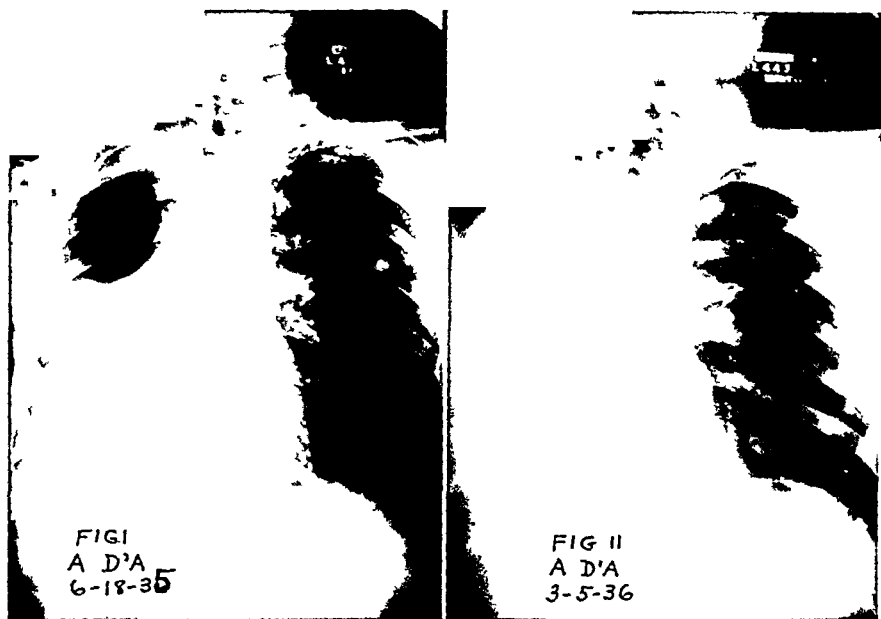


PLATE 1

For description see text

has been somewhat improved by the injections but do not think we have altered the ultimate prognosis This patient is now awaiting thoracoplasty, which will be done after he has passed his extended toxic phase

C A, white, female, age 25 Admitted July 9, 1934, with cough and expectoration of several months' duration Right artificial pneumothorax had been started three weeks before admission X-ray on admission Right Pneumothorax present, with complete collapse of upper lobe, and about 30 per cent collapse of middle and lower lobes However, cavity in the apex of the

lower lobe (3 cm diameter) is very little compressed. *Left* Normal. Sputum was positive (Gaffky VII), volume in 24 hours varied from 50 to 100 cc. Weight was 4 pounds below standard. Temperature was slightly elevated each day, to a maximum of 99.6° F.

The artificial pneumothorax was abandoned after 18 insufflations, there being no appreciable effect on the cavity. A right phrenicectomy was performed in November, 1934, and while the diaphragm was elevated and paralyzed as a result, no alteration occurred in the cavity. The sputum remained positive. In June, 1935, the roentgen status was as follows (figure III). *Right* There is a small cavity 1.5 cm in diameter at the apex of the upper lobe, and a 7 cm cavity in the apex of the lower lobe. *Left* A minimal exudative tuberculous infiltration had developed in the lower lobe, undergoing resolution, fibrosis and also slight focalized excavation. In March, 1935, an attempt was made to stenose the right lower stem bronchus by the introduction through the bronchoscope of 25 per cent acid acriflavine solution. However, in spite of these surgical procedures, the sputum remained heavily positive, and the 24-hour volume was from 50 to 60 cc. The temperature still exhibited its moderate instability.

Transthoracic injection of colloidal copper morrhuate was then advised. The first injection was given February 28, 1936, and the patient has been given four injections to date (April 3, 1936). She has had a moderately severe febrile reaction to two of the injections. The following changes have been noted since the use of this form of treatment: (1) The amount of sputum has been greatly reduced, the 24-hour volume now being only 3 to 6 cc. The sputum however is still positive. (2) There has been very definite improvement in the roentgen appearance of the chest. The cavity is not notably reduced in size but the parenchymal processes scattered throughout the right lung have completely disappeared and the wall of the cavity is thinner and more fibrous (figures IV and V).

#### *Comment*

We feel that there is real evidence that this patient has been notably improved by the injection of her cavity.

#### DISCUSSION

This paper is in the nature of a preliminary report, and given not to present a huge series of cases treated in this manner, but to bring the procedure to the attention of phthisiologists, so that it may be used more universally, and its practicability tested. It is easy to find cases of isolated cavities, not responding to less drastic forms of collapse therapy, in which transthoracic injection may be employed. The technique is



FIG III  
CA 6-7-35



FIG IV  
CA 3-5-36

FIG V  
CA 3-26-36

PLATE 2

For description see text

not difficult, but requires expert fluoroscopic guidance. We do not believe it a dangerous manoeuvre. The prognosis of cavernous tuberculosis is not good, as has been repeatedly demonstrated, and the five year mortality is astoundingly high. Any effort to eliminate the tuberculous cavity therefore has its justification in the mortality statistics for tuberculosis, and we urge that a procedure as simple as we have described, with potentialities for improvement, be more widely employed.

The authors wish to take this opportunity to express their gratitude to Dr J Gershon Cohen, roentgenologist to Eagleville Sanatorium, for his excellent and painstaking fluoroscopic work in connection with these cases.

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## ACACIA SOLUTION IN THE TREATMENT OF PULMONARY HAEMORRHAGE

OSCAR BERGHAUSEN

Subcutaneous injections of an aqueous solution of gelatin have frequently been used in the past to control recurring haemorrhages. Such injections are painful, frequently lead to abscess formation, and cause albuminuria. Intravenous injections of sterilized gelatin in 25 to 40 cc amounts of the 10 per cent aqueous solution have also been used, although leading to increased coagulability of the blood. No satisfactory explanation of this action of gelatin has been offered.

In 1915 Hogan (1) reported the successful use of 2.5 per cent gelatin solution in several injury cases and cases of shock following operations. Previously Czerny (2) had concluded that considerable amounts of acacia solution could be injected into normal animals without apparent injury. Bayless (3) introduced the intravenous injection of acacia solution for the treatment of wound shock during the World War and since then the method has been used rather generally. In 1921 Farrar (4) showed that 6 per cent acacia in 20 per cent glucose solution given at a slow rate intravenously is an aid in the maintenance of blood-pressure.

Experimental work by Andersch and Gibson (5) showed that 60 per cent of the acacia was retained by the liver and a smaller proportion by the spleen, kidney and muscles, following repeated injections of gum acacia solution into rabbits. In 1933 Hartman (6) reported favorable effects following twenty-seven intravenous injections of 30 gm acacia in 500 cc physiological saline solution, given to six different patients suffering from lipoid nephrosis. However, Andersch and Gibson (7) raised the question whether acacia should be given routinely to patients suffering from lipoid nephrosis and other conditions or whether it was a measure to be used when other methods had failed.

In 1932 the writer was asked to see a patient suffering from advanced pulmonary tuberculosis. She was too ill to have the newer surgical methods employed, and furthermore did not wish them employed. In August, 1933, she suffered from repeated severe pulmonary haemorrhages which ceased following the intravenous injection of 60 gm

acacia in one liter of physiological saline solution given in two injections. There was no recurrence until June, 1936, when the patient failed rapidly after a severe haemorrhage.

### *Case 1*

Miss A. S., aged 37, single, had haemoptysis in March, 1928, and at intervals thereafter. An X-ray examination in August, 1932, showed involvement at both apices and small cavities, especially marked in the upper left lobe with extensive infiltration of the left lower lobe. In August, 1932, dry pleurisy developed over the right base. On August 29, 1933, she had severe haemoptysis, repeated attacks, at times bringing up a cupful of blood. The usual remedies, including morphine sulphate given hypodermically and fibrogen internally, did not prevent a recurrence of severe haemorrhage. On August 30, 1933, 500 cc. of acacia solution was given intravenously with no general reaction. There was a recurrence of the haemoptysis on the second day, when a second injection of 500 cc. was given. With the exception of slightly blood-tinged sputum a few days later, there was no recurrence of the haemorrhage until her final illness in 1936. Ten days after the injection a maculopapular eruption appeared over the chest and abdomen. The eruption was scattered and accompanied by itching, lasted a week when desquamation occurred, leaving a reddish mark which faded gradually, apparently an allergic skin reaction following the injection of acacia.

Encouraged by this first result the writer did not hesitate to advise similar treatment in a second patient who had repeated pulmonary haemorrhages which could not be controlled by rest and the use of morphine given hypodermically and fibrogen internally. Apparently the patient had numerous haemorrhages before a physician was consulted. He was fond of working in his garden and frequently resorted to heavy lifting, the first haemorrhage followed such strenuous exertion. Although he had no elevation in temperature and the sputum examination for tubercle bacilli was negative, the diagnosis of pulmonary tuberculosis seemed justified after ruling out other possible causes of haemorrhage. The haemorrhages ceased two days after a single injection of the acacia solution.

### *Case 2*

A man aged 63 had been expectorating blood several weeks before Dr. H. H. Schulze was called on June 19, 1936. As much as a cupful of blood at a time was expectorated. It followed the lifting of a heavy barrel. Although there was no elevation in temperature the physician suspected the presence of pul-



monary tuberculosis and had an X-ray examination made by Dr Chas Goosmann who reported infiltration of the right middle lobe with increased bronchial tree markings extending upward to the right apex. There was no evidence of cavity formation, the aortic shadow was broader than usual. He suspected the presence of tuberculous infection but stated that an infarct might produce this same wedge-shaped shadow. With the recurrence of a severe haemorrhage on June 29, 30 gm of acacia in 500 cc physiological saline solution was given intravenously. This was followed by a chill within 30 minutes and then an increase in temperature to 103°F which lasted but a short time. Only two slight haemorrhages occurred, the last one two days after the injection. From then on morphine sulphate,  $\frac{1}{4}$  grain, and atropine sulphate,  $\frac{1}{150}$  grain, were given subcutaneously once or twice a day, hypodermic injections of obstetrical pituitrin, 8 M each, three injections of  $\frac{2}{3}$  grain emetin hydrochloride, calcium gluconate was given internally. On July 7 all medication except the calcium gluconate was discontinued. To date there has been no recurrence of the haemorrhage.

#### SUMMARY

Two cases of severe recurring pulmonary haemorrhage are reported in which the intravenous injection of 30 gm of acacia in 500 cc of physiological saline solution was followed by a cessation of the haemorrhage.

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## TUBERCULOUS PERITONITIS <sup>1 2</sup>

LORENZ W. FRANK

Tuberculous peritonitis either as a complication of pulmonary tuberculosis, or as the only clinical manifestation of tuberculosis, is a comparatively rare finding. However, in association with tuberculous enteritis it is relatively common. It has been noted that this condition often occurs when there is tuberculous involvement of other serous surfaces, notably the pleura. At the Colorado General Hospital there have been only three cases proved by autopsy or operation from 1924 to date. The Pathology Department of the University of Colorado has studied the autopsy material of 29 cases at the National Jewish Hospital showing tuberculous enteritis as a complication of pulmonary tuberculosis. Local peritoneal involvement was present in most of these cases. They found tuberculous peritonitis as the only complication in three cases. At this institution we have had four proved cases in which tuberculosis of the peritoneum was the only complication in a period of twenty years. It is more than likely that many cases occur in which the presence of this condition cannot be demonstrated clinically. Many tuberculous patients present symptoms that are suggestive, but since the condition usually runs a mild course and tends to heal, it cannot be proved. The incidence of tuberculous peritonitis seems to be decreasing. Olcott and Paccione (1) studied a series of 109 proved cases of tuberculous peritonitis, 90 of which were diagnosed clinically and 19 of which were found by necropsy. The average age of the seventy women in the entire series was 23.1 and of the thirty-nine men, 30.1 years. Of the clinical cases 73.8 per cent were found in women, while the necropsy incidence was rather higher in men (after allowing for the higher rate of necropsies in the male). It is generally stated that the disease is twice as common in females as in males and that it usually occurs between the ages of 20 and 40.

Whether the process is ever primary or not is problematic, if it occurs

<sup>1</sup> From the Lutheran Sanitarium, Wheat Ridge, Colorado

<sup>2</sup> Read at a meeting of the Denver Sanatorium Association, Denver, Colorado, May 26, 1936

with intestinal involvement this might be the case, the infection passing from the intestines. In connection with milary tuberculosis or other haematogenous spread, it is not uncommon to find tubercles on the peritoneum. The fallopian tubes are more often secondarily involved from the peritoneum than *vice versa*. The appendix, prostate or seminal vesicles may be the starting point or the infection may be spread from a softened peritoneal lymph node.

There are two main types of the disease, the exudative, accompanied by ascites, and the plastic type in which the intestines are matted together, their walls are thickened and the omentum may be rolled into a mass. This forms tumor masses which may be mistaken for other conditions such as tumors. The effusions are rarely large and are often sacculated by the matted abdominal viscera. Such a condition is a combination of the two types of the disease. The ascitic fluid may be haemorrhagic. Enlarged peritoneal lymph nodes (*tubercles mesenterica*) are sometimes present and may be a part of the plastic abdominal masses. The peritoneum is usually studded with small gray granulations, which at times seem to penetrate the intestinal wall. They are constantly present on the serous surface of tuberculous ulcers of the intestines. Both visceral and parietal peritoneum may be greatly thickened.

*Symptomatology* There is a great diversity of symptoms. The disease may be latent and discovered accidentally during operations. There may be low-grade fever or long periods of subnormal temperature. Otherwise, the patient may be asymptomatic, robust and well nourished. Indefinite gastrointestinal symptoms may be present, such as slight nausea, constipation or even obstruction, requiring operation. At other times, the disease begins suddenly with a chill followed by high fever and leucocytosis. The fever may reach 103° or 104°F. This is accompanied by abdominal pain which at times is so severe as to simulate acute appendicitis, cholecystitis, obstruction or strangulated hernia. The cases with slow onset may be mistaken for typhoid fever. Acute exacerbations may occur at long intervals, the whole process lasting months or years, ending in complete recovery or developing the more advanced lesions, such as tumors, due to thickened intestinal coils or rolls of omentum. Recurring ascites is also common. The larger plastic accumulations may caseate and ulcerate, a seropurulent or purulent exudate follows, this may be sacculated and secondarily infected. Alarming symptoms of toxicity result from such a state of affairs. This disease may at times occur in association with cirrhosis of the liver, ovarian

tumors, trauma or in hernial sacs, when this occurs the picture is still more complex.

*Differential diagnosis* is difficult. Local signs are deceptive. It is easy to confuse this condition with ovarian cysts or with malignant masses and ascites resulting from a papillary ovary or an adenocarcinoma of the ovary. These conditions are usually not accompanied by fever. Differentiation from cirrhosis of the liver, Banti's disease or chronic nontuberculous peritonitis must also be considered. Here the intracutaneous tuberculin test and guinea-pig inoculation, as well as a history of old tuberculous lesions, are helpful. If there is an associated salpingitis or if there is tuberculous involvement of the lungs, pleura, pericardium, epididymis or seminal vesicles in a patient who has irregular periods of fever and indefinite gastrointestinal symptoms, tuberculous peritonitis should be suspected.

*X-ray* There are no distinctive roentgen signs in this condition. However, a flat film of the abdomen without contrast media may reveal dilated coils of intestines which may point the way to the recognition of lesions which are producing partial or complete obstruction. The barium meal or enema may show filling defects or abnormalities of motility. These indirect signs may be helpful in arriving at a diagnosis.

*Prognosis* According to Bernhard (2) the mortality in all cases of tuberculous peritonitis, irrespective of their type, was 5 per cent. Mayer (3) says that the serous exudative type generally responds to light irradiation, both in children and in adults. The dry proliferative form, usually adhesive, is more refractory. When there have been ulcerations and large caseous lymph nodes, as commonly seen in children, the results are most unsatisfactory. When the disease is of long standing, healing is more difficult than when irradiation is begun a short time after onset.

*Treatment* It is difficult to evaluate the results of any form of special treatment in a disease which often runs a mild course and probably heals many times spontaneously. Many cases seem to recover with rest and general measures alone. Heliotherapy seems to be the most widely accepted form of special treatment, and certainly has a marked effect in the relief of pain and other abdominal symptoms. However, not all cases bear this form of treatment well, their complaints are at times aggravated, especially if it is applied while the fever is high or while there are other signs of toxicity. Brody (4) has concluded that daily exposure to sunlight for a period of from 3 to 6 hours, as has been

prescribed heretofore, is excessive. This agrees with our experience and we have reduced the time of exposure considerably.

Röntgen therapy is useful in some cases. If a focus of infection such as an appendix or fallopian tube can be demonstrated, its surgical removal may lead to a cure. Surgery must also be resorted to in cases of intestinal obstruction.

Merely opening the abdomen has often resulted in a clinical cure, particularly in cases associated with ascites. This can also be said of pneumoperitoneum.

#### COMMENT

From a diagnostic point of view it should be emphasized that tuberculous peritonitis is a condition which is difficult to diagnose clinically. As a pure complication of pulmonary tuberculosis it is not often recognized clinically, at least not until it is advanced. This is due to its protean clinical course and symptomatology. The frequency with which it is found in association with tuberculous enteritis demonstrates that it is much more common than it is ordinarily thought to be.

Unexplained abdominal symptoms occurring in cases of pulmonary tuberculosis undoubtedly are often due to this condition. Spontaneous healing probably occurs often. Since progression of pulmonary lesions may occur while the peritoneal condition improves, and *vice versa*, frequent and complete examinations are necessary in order to remain fully informed about the course of the disease.

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# MANIFESTATIONS OF UNDULANT FEVER IN THE RESPIRATORY TRACT

OREN A. BEATTY<sup>1</sup>

The increase in number of cattle and hogs, together with long distance transportation, has increased their morbidity rate of Bang's disease. Bang's disease has become such a problem that the United States Department of Agriculture has begun a nation-wide project of Bang's disease testing and eliminating reactors in cattle. The number of reactors in the United States during 1935 was 13 per cent of 3,300,000 cattle. The number of reactors to Bang's disease exceeded the number of tuberculin reactors, although more than 25,000,000 tuberculin tests were applied. This suggests a tremendous probable source of infection in those that have not been tested. When this is generally realized *Brucella* infection in man will be given more consideration. Undulant fever in man was once considered a rare condition but has become more prevalent in the past decade and at the present time is a major public-health problem.

Very little has been written in this country in regard to symptoms of this disease referable to the respiratory tract, except in a general way. Bogart recently called attention to the sparsity of reports of pulmonary manifestations and reported four cases of undulant fever in which pulmonary symptoms occurred with demonstrable roentgenological changes. This is a study of forty-seven cases of undulant fever with particular reference to respiratory symptoms and an X-ray study of twelve cases.

## SYMPTOMATOLOGY

In general, two forms of undulant fever may be recognized, the acute and the chronic. The literature gives other finer distinctions but most cases are readily grouped into acute or chronic. In the acute cases the onset may be gradual with malaise, general aches and pains, backache, and aching in the back of the neck, and chilliness at times. These symptoms may progress into acute conditions, or the onset may be with

<sup>1</sup> Chest Clinic, T. J. Sampson Community Hospital, Glasgow, Kentucky

severe chills and fever of 103° to 104°F and complaints of general aches and pains, particularly backache and aches in the back of the neck. Many patients complain of aching in all parts of the body, even in skin, teeth and scalp, and many complain that the skin of the neck is so sore that merely touching it is very painful. Marked loss of weight and severe night-sweats characterize the acute stage. The acute stage may last from two weeks to two months with exacerbations and remissions of pains and fever, but I have not observed that the exacerbations and remissions occur at any particular time of the day. In many patients who are not aware of fever the temperature ranges from 103° to 104°F.

The chronic stage may follow the acute and may last for several years. It may be characterized by backache, aches in the back of the neck, choking or smothering sensations at times, palpitation at rest or on exertion, fatigue on exertion, extreme nervousness, pains in shoulders, along rib-borders, or in the region of the ovaries, and inability to do a day's work. These symptoms also occur in periods of exacerbation and remission and may or may not be accompanied by fever. In some cases of proved chronic undulant fever there has been no acute stage according to the patient's history. The above symptoms of the chronic stage are observed in the majority of cases, but there are innumerable other symptoms observed in individual cases. It is in the chronic stage that so many present themselves for chest examinations. These cases are characterized by burning sensations and pains in the chest, cough without expectoration or with mucoid or mucopurulent expectoration, occasional haemoptysis, fatigue on exertion, inability to perform a day's work, hoarseness, afternoon fever and night-sweats, they are convinced that they have pulmonary tuberculosis or some other pulmonary disease. Undulant fever manifests itself practically throughout the respiratory tract, particularly in the bronchi and the larynx.

Of forty-seven cases diagnosed as undulant fever, thirty-two were studied sufficiently to tabulate their symptoms. Of these, thirty-one had symptoms referable to the respiratory tract: eighteen had cough, sixteen expectoration, five haemoptysis, twenty-six pains in the chest, twelve burning sensations in the chest, twenty-three choking or smothering sensations, fifteen weakness of voice, fourteen hoarseness, five nasal discharge, eight postpharyngeal discharge and seven sneezing. The symptoms referable to the upper respiratory tract were overlooked in the early cases.

## DIAGNOSIS

A diagnosis is first suggested by the clinical symptoms and particularly by the absence of physical signs of any other disease. It is important to take a careful history in order to bring out all the symptoms, since the symptomatic manifestations of undulant fever are rather characteristic. There are many diseases with which undulant fever may be confused, particularly tuberculosis, influenza, typhoid fever and malaria. The respiratory symptoms of undulant fever, with afternoon fever occurring in the asthenic type of patient, are easily mistaken for tuberculosis, particularly in the absence of an X-ray plate of the chest and sometimes even in the presence of such an X-ray plate. Frequent attacks of fever simulating influenza in the otherwise healthy individual are often diagnosed as influenza. When attacks of undulant fever occur in the warmer months, and particularly in the presence of outbreaks of typhoid fever, it is often diagnosed as typhoid in spite of negative cultures and Widal's. It is not infrequent that patients state they have not been well since having had typhoid fever several years ago. These patients should be examined for undulant fever and, if undulant fever is found, it is reasonable to suppose that the original disease was undulant fever. The acute stage of undulant fever with frequent chills is often called malaria and treated as such. Undulant fever should be in mind in the study of the above four conditions particularly when the diagnosis cannot be confirmed readily by the ordinary laboratory aids.

The agglutination and intracutaneous skin tests are invaluable laboratory aids in making a diagnosis. Ordinarily an agglutination test positive in 1 to 80 dilution or above is considered diagnostic, but so many patients are seen in whom several positive agglutinations below the 1 to 80 dilution are obtained before one in a higher and so-called diagnostic dilution that it seems a positive test in any dilution should receive serious consideration, especially in the presence of clinical symptoms. Angle states that when the agglutination titre is low or absent the patient may be a victim of this disease. Simpson states that agglutinins are absent in five per cent of the cases. Harris thinks much harm has been done by laboratories stating that only tests in dilutions of 1 to 80 or higher are of significance. He further states that eleven of seventy-five cases he observed were negative on repeated agglutination tests. A positive test in any dilution should call for further diagnostic efforts, and so should a negative test with clinical symptoms. The skin



test may prove to be of more value than the agglutination test, since the agglutinating titre of the blood may change rapidly. The test is made with 0.5 cc to 1 cc of *Brucella* antigen intracutaneously. Pseudoreactions are at their height at twenty-four hours and begin to subside before forty-eight hours. A positive reaction is at its height by the fourth day and should gradually subside and persist in the form of a reddish-brown discoloration for four weeks or longer. In many positive cases of undulant fever in which skin tests are done, an immediate local reaction is obtained which may be a specific bacterial phenomenon, which may have diagnostic significance. Recovery of the organism from the blood-stream is diagnostic, but the procedure is rather difficult to carry out in the ordinary laboratory.

#### PHYSICAL FINDINGS REFERABLE TO THE RESPIRATORY TRACT

The nasal mucosa has not been examined routinely. The pharynx, in occasional cases, shows moderate or mild injection. The larynx, in many cases, shows injection of the epiglottis, arytenoids, and ventricular folds. This injection may vary from a mild condition to that of diffuse redness with a granular appearance and slight to moderate swelling. The vocal cords are not injected. Physical examination of the chest is negative as a rule in the chronic case. One case reported here had impaired percussion note with deep-seated moderately coarse râles after cough. Bronchiectasis was suspected but not proved. Another case had a few deep-seated fine moist inspiratory râles from the third to the sixth vertebral spine on the left. In acute cases, simulating pneumonia, a small patch of dulness with bronchial breathing and sparse moist inspiratory râles may be found. Also a friction rub may be heard occasionally, especially in the pneumonic cases and those that have pleuritic pains. One case had a pleural effusion.

#### ROENTGENOLOGICAL FINDINGS REFERABLE TO THE RESPIRATORY TRACT

In a study of the X-ray appearance of the chest of the undulant fever patient we see variations in the amount and distribution of changes from the normal. The most constant change noticed is hilar infiltration with a generalized peribronchial infiltration as shown in figures 1 and 2. In some cases the hilar infiltration may predominate over generalized peribronchial infiltration, and in some the generalized peribronchial infiltration may be greater in one lung than the other or greater in one base than in the other. The next most frequent change noted is pleural

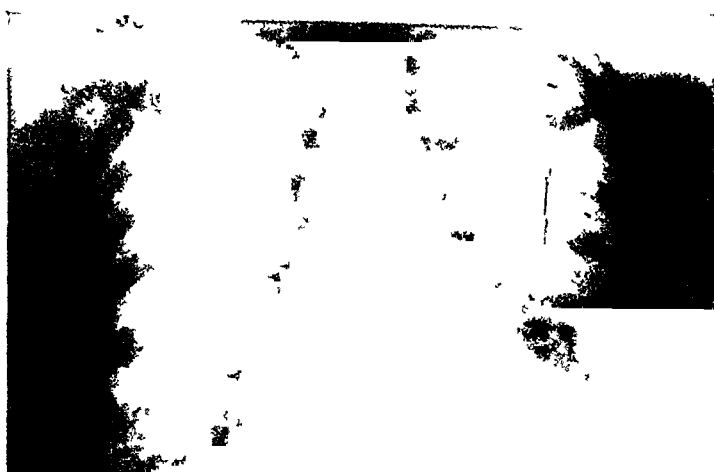


FIG. 1 Generalized peribronchovascular infiltration throughout both lung fields with moderate hilar infiltration on both sides

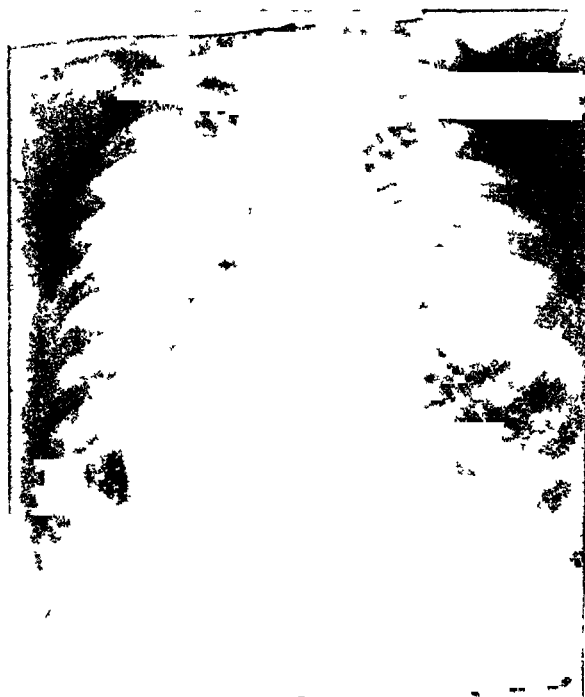


FIG. 2 Generalized peribronchovascular infiltration throughout both lungs with moderate hilar infiltration on right

One case of pleural effusion and one case of diaphragmatic pleurisy with adhesions were seen. No X-ray was obtained of the patient with pneumonia during the pneumonic stage.

#### DISCUSSION

Due to circumstances only twelve, of forty-seven cases, have had X-ray examinations of the chest. One patient is included who could not be definitely diagnosed as undulant fever. Several other patients presented as severe chest symptoms as those who were X-rayed. It is believed that they too may have presented pictures similar to the above. Of these forty-seven cases, thirteen had been previously diagnosed or strongly suspected as having pulmonary tuberculosis. In the majority of cases that present themselves to chest clinics for examination no tuberculosis is found. In nontuberculous chronic chest conditions undulant fever should receive serious consideration in the differential diagnosis. All twelve patients whose chests were X-rayed showed more or less marked enlargement of the hilar shadows and some scattered peribronchial infiltration, usually bilateral and frequently more pronounced in the basal portion.

A history of haemoptysis is not infrequently encountered in these cases of undulant fever. The author did not witness the haemoptysis in any case, but was able to get a definite history of haemoptysis in each case reported. In one case the material expectorated the day following haemoptysis was viewed and this was mixed throughout with old and fresh blood. Haemoptysis occurs frequently enough in the history of these cases to warrant the belief that it may occur in the cases with pulmonary X-ray changes.

Another symptom frequently encountered in the history is hoarseness and weakness or loss of voice. This may be easily explained from examination of the larynx which shows in the majority of the cases examined a definite laryngitis. Sneezing, postpharyngeal discharge and nasal discharge or rhinorrhoea occurred in many of the later cases. These symptoms were overlooked in the first cases encountered, until one long-standing case of rhinorrhoea, which had not yielded to treatment cleared up when the patient's undulant fever was treated with undulant fever vaccine. This directed attention to the nasal symptoms found in undulant fever.

Another respiratory symptom observed in many cases is a smothering or choking sensation. If this condition is severe many patients

think they are going to die, and afterwards say they could not live through another attack. The severity of the attack impresses witnesses and onlookers. To the witnessing physician there is not the respiratory difficulty that is observed in a severe attack of asthma or severe cardiac condition. The concurrent cyanosis is not typical and it is a rather murky or dirty cyanosis. Palpitation is complained of and tachycardia is present during the attack. The attack may last from thirty minutes to two hours or longer and may simulate effort syndrome but it is probably more severe in many cases.

#### CONCLUSIONS

- 1 Undulant fever is a major public-health problem
- 2 It manifests itself frequently by respiratory symptoms and signs
- 3 Demonstrable X-ray changes are noted frequently, consisting of peribronchial infiltration, thickened pleura, pleural adhesions and pleural effusions. Pneumonias occur but are not demonstrated here roentgenologically
- 4 Chronic nontuberculous pulmonary conditions should include undulant fever in the differential diagnosis
- 5 Undulant fever should receive consideration as the aetiological agent of such conditions as rhinorrhoea, "common colds," influenza, sinusitis, pharyngitis, laryngitis, bronchitis and pneumonia when the aetiology is not definitely known. Haemoptysis may also be included

Appreciation is expressed to Dr O O Miller, Louisville, Kentucky, for the use of one X-ray picture, and to Miss Mary Foulk, clinical nurse, and Miss Katherine Morrow, technician, for their help in the study of these cases.

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## EDITORIAL

### *The Value of Tomography in the Diagnosis of Pulmonary Lesions*

Dr J B McDougall's and Dr J H Crawford's article on "Tomography" (1) with special reference to its value in the diagnosis of pulmonary lesions is most instructive and suggestive. I know of no clearer statement of what Tomography is, and what may be expected of it when studying pulmonary lesions.

Before expressing any opinion I wish to state that it has not been my good fortune to have used the tomograph personally. After working with any instrument one's opinion may change or crystallize.

To those who have had to depend upon single films this will be a great advance. For those who have had the advantage of stereoscopic films it will not be necessary so often.

The bronchial, the pulmonary and the venous systems are beautifully described, but if one wishes to study the normal anatomy of a healthy chest, tomography, in my opinion, cannot compare with good stereoscopic films. This is also true of pulmonary exudates, which must be diagnosed and accurately localized. Such lesions are common in the upper third of the lower lobes, and the trunks to these important areas have not been described in this article. I doubt that they could be shown by tomography.

For many years it has been my privilege to study pulmonary anatomy and pathology by means of stereoscopic films. I have had hundreds of cases come to autopsy. It is daily practice to describe the trachea, the right and left bronchus, the eparterial and the hyparterial bronchus, the pulmonary arteries and to note their dislocation and some of their pathology. With this anatomy as a basis the pulmonary lesions are quite accurately described and localized with regard to the part of the lobe involved. This is accomplished in the vast majority of cases studied. I cannot conceive that this could be done as accurately by tomography as by stereoscopic films.

When dealing with very dense lesions or tissues of homogeneous density stereoscopic films are valueless and it is my hope that tomography will be able to solve the difficulties encountered in such cases. This

is illustrated by case 6, figure 12 (1) When positive sputum persists after thoracoplasty, it is often impossible to localize by stereoscopic films cavities concealed in the dense mass of tissue The authors have demonstrated that tomography is most helpful in such a case

We are all indebted to Doctors McDougall and Crawford for this clear presentation of a new instrument and its usefulness

K D

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# THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS OF TUBERCULOSIS

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## CONTENTS

	PAGES
Treatment ( <i>concluded</i> )	1- 3
Diseases Other than Tuberculosis	3-17
Prognosis and Prevention	17-21

**Total Pneumonectomy**—A detailed description of the technique of pneumonectomy for both right and left lung is presented. The method used is based upon a series of 10 total and 20 partial pneumonectomies. Of the 10 total pneumonectomies, 4 were on the right side and six on the left. Eight were operated upon for tumors of the lung and 2 for unilateral tuberculosis. In the group there was one death each due to diffuse lobular pneumonia, metastasis of the tumor to the brain, tuberculosis of the remaining lung, and pulmonary embolism.—*The Surgical Technic of Total Pneumonectomy*, W. F. Renshoff, Jr., *Arch Surg*, February, 1936, xxxi, 218—(L F B)

**Contralateral Spontaneous Pneumothorax Complicating Lobectomy**—The author reports 3 cases, two of which died, of contralateral spontaneous pneumothorax occurring during lobectomy. Although no definite opening could be found at autopsy, it was concluded that a small opening was made through the mediastinum at the time of operation. Death in the third case was prevented, when it was found that the lungs did not expand well on discontinuing positive pressure anaesthesia, by inserting a catheter between the ribs on the contralateral side, allowing the air to escape under water and continuing the positive pressure anaesthesia. It is conceivable that contralateral pneumothorax might result from a

rupture of one or several alveoli on the unoperated side if the patient's breathing is labored or too high positive pressure is delivered through the anesthetic apparatus. Any change in the respiratory action, associated with failing of the pulse should immediately suggest contralateral pneumothorax. Increased positive pressure and an outlet for air on the contralateral side is the suggested procedure of choice.—*A Consideration of Contralateral Pneumothorax as a Complication of Intrathoracic Operations*, H. B. Stephens, *J Thorac Surg*, June, 1936, v, 471—(L F B)

**Scalenotomy**—The author employed scalenotomy and phrenicocoelectrolysis in those cases in which pneumothorax was tried with negative results, and plastic operation in some form or plombage was not indicated, or as a complementary operation in incomplete pneumothorax when plastic operation or cauterization could not be resorted to. The direct effect lay not simply in an increased collapse, but rather in a considerably reduced respiratory movement in that half of the thorax. Not much change in the shape of the thorax could be seen in a radiograph, but the decreased movement could easily be seen by direct illumination. Usually a marked improvement could be observed after the operation, cough, temperature and general condition were usually favorably affected. As a rule, expectoration increased



# THE AMERICAN REVIEW OF TUBERCULOSIS

immediately after the operation and then diminished, and tubercle bacilli often disappeared from the sputum. Roentgenologically the cavities disappeared and the tuberculous process became more fibrous—*Scalernatorni in Pulmonary Tuberculosis Observations at Sordtråsk Sanatorium, A Tornblom, Acta Tuberc Scandnav, Fasc 4, December, 1935, ix, 329—(F B S)*

## Abdominal Compression in Treatment of Pulmonary Tuberculosis—

In a series of 211 patients with fibroid pulmonary tuberculosis diaphragmatic elevation was accomplished by means of a special abdominal support, held in place by a special piece, straps and buckles. Such supports have been worn for from two to thirty months, day and night, except in the presence of intestinal tuberculosis and malnutrition, when removed for short periods. Eighty-two patients were ambulatory practically throughout, 33 working, while the others had sanatorium care or its equivalent. *Results* Symptomatic relief from dyspnoea and difficult expectoration was the rule, especially in those with the fibroid type of disease and a well-developed abdomen. Ninety patients gained in strength and general well being. The unsatisfactory results occurred in cases with acute extension or soft, caseating lesions. There was usually a decrease in coarse râles, especially at the bases. X-ray films showed an average elevation of the diaphragm of 1.2 cm. Structural (pathological) improvement occurred in 43 (17 ambulatory), as evidenced by decrease or disappearance of cavities and retrogression of other lesions. In 4 patients whose supports were removed, an increase of cough and dyspnoea followed almost immediately. Two apical cavities which developed under pneumothorax closed after reexpansion and abdominal compression. Capacity to exercise safely was noted in 26 with cavitation and fibrosis. Vital-capacity studies showed an initial reduction with later gradual return toward normal. There was a temporary increase in respiratory rate in most. *Physiological considerations* These are discussed to some degree and some hypotheses put forward. Gordon favors this measure to counteract deep vertical pulmonary excursions, which he regards as detrimental, and to reduce pulmonary ventilation (?) which favors the progression of disease (?). *The Mechanism and Effects of Abdominal Compression in the Treatment of Pulmonary Tuberculosis, B Gordon, New England J M, January 30, 1936, ccxiv, 195—(A P)*

**Oxygen Administration by Nasal Catheter**—It is now generally agreed that

for prolonged oxygen administration its proportion in the inhaled air should be between 35 and 60 per cent, that is, about 30 to 55 per cent in the alveolar air. Higher proportions are irritant and induce dangerous inflammation. The widespread impression that nasal catheter administration cannot attain these concentrations is challenged by recent American studies, but to be effective a flow of 4 to 16 liters per minute is required, which is far beyond what is generally used. This paper describes apparatus presenting new features and records experimental data on alveolar oxygen concentrations with this apparatus. *Description of Apparatus* Two catheters, each 3½ inches long, are used, about 3 inches of each lying within the nose, which may require preliminary cocaineization. The catheters are made of ordinary cycle valve tubing, soft and thin-walled, and of minimum cross section. The catheter carrier is an adaptation of the laryngologist's head mirror strap, buckling at the side and with padded knots on either side of the bridge of the nose. A corrugated rubber forehead pad is substituted for the ordinary wool and wash leather. The carrier is strapped on before introducing the catheters, which should be lubricated with liquid paraffin. There are also *flowmeters* and *humidifiers*, the former being of the type of water flowmeter with a small colored bead floating on the top of the column. The springs holding the bung allow it to lift if pressure is excessive. A newer model with a slightly taller bottle serves as a humidifier. Oxygen cylinders should be fitted with pressure regulators automatically reducing the pressure to 3 to 5 pounds. Effective nasal catheter administration demanding a considerable flow, large cylinders are most economical, lasting about six hours at 8 liters per minute, 1 cubic foot yielding 28.3 liters. To facilitate transportation, a stand of the porter's barrow type is used, can be wheeled easily about and loading or unloading is not difficult. The twenty-four hour cost in oxygen is roughly 10s to £2 (or \$2.50 to \$10.00 in United States money). *Experimental Work and Results* The determinations of oxygen concentration in alveolar air were made upon two normal subjects, samples being collected by the syringe and whistling method. They were analyzed in a Haldane gas analysis apparatus. For each subject two sets of determinations were made, at 4, 8, 12 and 16 liters per minute, through the mouth. Respiratory rate has made, at 4, 8, 12 and 16 liters per minute, through the mouth. Respiratory rate has previously been shown to make little difference. *Summary* 1. Apparatus, new in several respects, for the nasal catheter administration of oxygen has been described. 2. Alveolar oxygen concentrations at flows

from 4 to 16 liters per minute, ranged from 29 to 58 per cent, (Mean values). Thus, the fact that optimal concentrations of oxygen for prolonged administration can be obtained by the apparatus has been demonstrated—*Oxygen Administration by Nasal Catheter*, H I Macrae & A Robson, *British M J*, January 25, 1936, No 3916, 154—(A P)

**Maggot and Allantoin Treatment.**—Seven cases, in addition to the one previously reported of maggot therapy in tuberculous and nontuberculous suppurative lesions of the lung and pleura, and one case treated with allantoin alone, are reported. Of 3 cases of tuberculous empyema with broncho-pleural, pleurocutaneous fistula, one is cured following thoracoplasty, one is permanently improved and awaiting thoracoplasty, and one is dead of contralateral disease after showing temporary local improvement. One patient with tuberculous osteomyelitis and bronchocutaneous fistula showed temporary improvement and died of disseminated disease. One patient with recurrent nontuberculous empyema was cured. One patient with gangrene of the lung showed temporary improvement and died of pulmonary haemorrhage unconnected with the specific therapy. One patient with abscess of the lung was cured. One patient with tuberculous empyema, treated with 0.5 per cent solution of allantoin irrigations, was unimproved, and died. Maggots will ingest living tubercle bacilli, and there is some clinical evidence that they are not simply excreted unchanged—*Maggot and Allantoin Therapy in Tuberculosis and Nontuberculous Suppurative Lesions of the Lung and Pleura*, A Bethune, *J Thorac Surg*, February, 1936, v, 322—(L F B)

**After-Care of Tuberculosis in London**—The organization of after-care in London is unique chiefly in the enormous size of the population and the division of responsibility into borough units. In the main, the "voluntary" principle is followed of a Care Committee of voluntary workers in intimate association with a dispensary and the officers of the borough and county public health services. In many instances, however, a previously voluntary secretary has been replaced by one employed and paid for by the borough. Only three voluntary care-committee secretaries remain, all highly efficient and experienced. Of the 28 London boroughs, 23 have voluntary Care Committees. Hackney and Stoke Newington have a joint committee, Greenwich and Bethnal Green, none, and Bermondsey and Lambeth, almoners who are officers of the borough

councils. Generally speaking, the originating agent is the Tuberculosis Officer or Care Committee Secretary. Also, what happens to the patient after his discharge from a sanatorium is more important than his treatment while there. At the London County Council institutions, it is now customary for a visiting almoner to visit them periodically in order to link up treatment and after-care. This has long been the custom with the Brompton Hospital and the sanatorium at Primley. Some emergency funds should be available to a Care Committee. *Special settlements and workshops*. Prominent among these are the industrial settlements at Papworth and Preston Hall and the training school for boys at Burrow Hill. To be suitable for a settlement, a patient must be able to earn a wage sufficient to support himself and dependents, if any. He therefore must be able to work a full day and be technically efficient. He must also have character. McDougall estimates that not over 4 per cent of admissions really prove suitable. Burrow Hill, which does not attempt to settle, obtains 30 per cent of successes. The Spero Workshops, like Papworth and Preston Hall, attempt to run a business on commercial lines and pay trade wage scales. Their contribution is limited and achieved at the expense of much work and worry. Handicraft classes are now held in 15 boroughs, those at Woolwich and Deptford being of special importance. *Rehousing*. A growing factor in after-care policy is the rehousing of overcrowded households containing an active case of tuberculosis. This usually means translation from a slum district to a new suburban estate. The principle of letting such houses to a tuberculous family is not universally approved. However, the experience of Londoners at the new Dagenham estate is encouraging. Transportation difficulties for workers and lack of nearby cheap markets are two real disadvantages. *Other functions*. The Council assists in boarding out children in close contact with infectious patients and to send away mothers for treatment. Borough Councils may incur expenditures for extra nourishment upon proper recommendation, and arrange with School Care Committees for school meals. The London County Council has also recently arranged to provide clothing on loan to patients in or going to institutions—*The After-Care of the Tuberculous in London*, N D Bardswell, *Tubercle*, April, 1936, xvii, 289—(A P)

**Psychosis and Pulmonary Tuberculosis**—Insanity among the tuberculous is mostly of the catatonic type. A hallucinatory type and those with simple delirium

are relatively rare. Up to the present it has not been definitely demonstrated that tubercle bacilli act as a causative factor in insanity, and a tuberculous psychosis is a symptomatic psychosis has been generally denied. In 9 cases of schizophrenia the development of an acute progressive tuberculosis was observed, and in all of these cases the catatonic symptoms which developed after the tuberculo had become manifest, were probably the result of a tuberculous toxemia. Referring to the usual modern concept as to the aetiological importance of intoxication in causing psychoses, the author resumes in his 9 cases that the tuberculo is related as the causative factor in producing the psychosis. With the development of a florid tuberculous process, with tissue destruction and signs of toxemia, these cases developed a symptomatic psychosis, while the majority of the inmates ran true to form.—*Über die Beziehung zwischen Tuberkulose und Psychose, II. Siesler, Klin. Wochenschr., May 25, 1935, x, 754—(F. G. K.)*

**Tubercle Bacilli Absent in Dementia Praecox**—Previous publications have shown negative cultural findings of tubercle bacilli in the blood and cerebrospinal fluid of cases of dementia praecox. In view of the fact that this does not necessarily exclude the tubercle bacillus as an aetiological factor in dementia praecox but supposing the bacillus to be present in a filterable form and consequently detectable only by animal experimentation, a series of guinea pigs were inoculated with cerebrospinal fluid and blood from these cases. Twenty nine specimens of blood and twenty seven of spinal fluid and two brain specimens were examined. Ten blood specimens from human cases of tuberculosis and two from experimental tuberculosis in guinea pigs were examined as controls. The specimens were inoculated intramuscularly into guinea pigs, which were then treated with an acetone extract of tubercle bacilli, according to the method of Valtus and Nègre. The animals were observed and tuberculin tested up to seven months, and upon autopsy their organs were examined microscopically and culturally and were reinoculated into successive guinea pigs as far as the fourth and fifth generations. In this way 311 animals were used. In no case of dementia praecox could tubercle bacilli be detected. In the control animals two yielded positive results. Tuberculosis may be excluded as an aetiological factor in dementia praecox.—*Sur les relations entre démence précoce et la tuberculose. Contrôle du sang, du liquide céphalo-rachidien et du cerveau des déments précoces par l'expérience sur*

*Larimal. A. Becl., Compt. Rend. Soc. Biol., October 19 1935, cxx, 311—(M. T. W.)*

**Fistula-in-Ano**—It is doubtful if for even bodies account for more than a very small percentage of cases of fistula in ano. They consist mostly of fish and rabbit bones, pieces of wood and metal and seeds. A small neglected fissure is liable at any time to penetrate the muscular wall of the rectum resulting in a small direct fistula with its internal opening at the base of the fissure. The suppuration of anal glands is the commonest cause of all. These glands occur near the lower end of the anal canal as tubular, branched structures passing into or through the muscular coat and ending in connective tissue. They often pass through the internal sphincter and terminate in the ischioanal fossa. These vesicular glands which correspond to the odoriferous glands in certain animals, act as a path for infectious organisms to reach the connective tissues. Congenital cysts occur at the site of the postanal dimple, which is present in 20 per cent of human beings, suppuration resulting from trauma or excessive growth. They always occur just over the tip of the coccyx, and the presence of hairs is conclusive. Such cysts must be completely removed or they will reform. Tubercle accounts for about 20 per cent of all cases of fistula in ano. Tuberculous fistulae are distinguished by undermining of the skin, thin serous discharge, and bluish or purplish coloration. The vast majority are secondary to pulmonary tuberculosis. It is useless to search for tubercle bacilli in the purulent discharge, and either guinea pig inoculation or biopsy of the wall of one of the tracts, together with special staining, is the only method of proving the diagnosis. Injury and trauma cause a variable proportion of fistulae, and include the injection treatment of piles faultily carried out, and the insertion of radon seeds or radium needles near the rectum for carcinoma. In practically all cases the initial lesion is an abscess. If this is opened early and free drainage established either externally or internally, about 70 per cent of cases will heal without fistula formation. Tuberculous fistulae should be conservatively treated. Drainage of the tracts should be established by the simplest method, and the patient at once sent to a sanatorium or put under proper hygienic conditions, local treatment being entirely subordinate. When the patient is in good condition, the fistula can be treated in the usual way, but a diathermy knife or actual cautery is preferable to the scalpel, in order to minimize a dispersion of bacilli into healthy parts.—*Fistula in Ano, J. P. Lock-*

hart-Mummery, *Lancet*, March 21, 1936, cccxv, 657—(A P)

**Trauma of Lung**—Pulmonary trauma is probably not uncommon, even without external evidence of injury, such as bruises, muscular hæmatomata and fractured ribs. Hence, lung damage by external violence assumes a place of importance in clinical and forensic medicine and offers a problem in physics inviting investigation. Text-books of medicine give scanty notice to violence in the causation or exacerbation of pulmonary disease, although some reference is made to its rôle in pneumonia and tuberculosis. Cooke, in 1934, attempted to classify lung injuries from a clinical standpoint. In his *pneumothorax type* there is simple rupture of a few alveoli and the visceral pleura, without necessarily such evidence of injury as hæmoptysis or hæmothorax. In *parenchymal rupture*, this may result in either bronchopulmonary hæmorrhage or subpleural ecchymoses and bruises. In a *combined type*, there may be both hæmorrhage into the lung and pneumothorax or hæmopneumothorax. Physical explanation of the variations observed is difficult. It is assumed that the lungs must be in inspiration and the glottis closed. None of these cases showed fractured ribs or external bruises. The fact that extensive visceral damage can be produced without external evidence is important. The possibility of a reactivation of latent tuberculosis or a renewed rapid progression of an active lesion is obvious. Also, it is often difficult to convince judges and juries that bruises are not necessarily present in cases of violence and that they bear no necessary relation to the severity of the violence.—*Pulmonary Trauma*, W E Cooke, *Brit M J*, March 7, 1936, no 3922, 461—(A P)

**Rupture of Diaphragm**—The term, *rupture of the diaphragm*, should be reserved for those cases in which loss of continuity of this structure is the result of sudden increase in intraabdominal pressure following trauma or violent effort. This definition excludes stab- and puncture-wounds of the diaphragm, whether by foreign bodies or by costal fragments. A distinction should be drawn between true rupture of the diaphragm and hernia of the diaphragm. Rupture of the diaphragm occurs chiefly in healthy young adult males, and rarely in infants or old people. Most frequently it is by contusion, much less common are ruptures by effort. Predisposing factors include congenital defects in the diaphragm, and tumors and inflammations of that structure. A very full stomach will also predis-

pose to the condition. Experimental work done on cadavers indicates that an open glottis, at the time of the effort of trauma, is almost a prerequisite for rupture of the diaphragm, and further that relaxation of the abdominal muscles favors it. In 126 out of 146 cases rupture occurred unilaterally on the left side. This predisposition may be due to the fact that the viscera on the left are pneumatic, and are thus better suited to transmit increases in intraabdominal pressure than is the liver. Also, these organs are more easily forced into the thoracic cavity. It is not unlikely that small ruptures of the right side of the diaphragm pass unnoticed because they are susceptible to spontaneous healing. This cannot occur when herniation has taken place. Ruptures may be tendinous, muscular or musculotendinous. True ruptures of the diaphragmatic muscle are very rare, most such cases being the result of tears in it by fragments of ribs. Rupture may occur at the normal hiatuses in the diaphragm, but not commonly. The most frequent site of true rupture of the diaphragm is at the costophrenic insertion, and more particularly at the anterior and posterior axillary lines. This may be due to the fact that the greatest strain occurs here when the base of the thorax enlarges as a result of the increased intra-abdominal pressure. Indeed, in certain instances herniation between the ribs may occur. Aside from its frequency and lateral situation, this type of rupture of the diaphragm is characterized by its frequently large size (10 to 35 cm), its tendency to gape, and its close proximity to the ribs. This last-named fact favors the surgeon when repairing small lesions, for he can support his sutures on the ribs, but in cases with large rents the rigidity of the ribs often makes it difficult to approximate the edges of the rupture. Occasionally the diaphragm may rupture at its anterior border under the xiphoid process. In these cases the peritoneum, pleura and pericardium may all be involved. Ruptures posteriorly situated are not common, and usually involve the oesophageal hiatus. These usually partake of the nature of spontaneous hernias. Lastly, rupture may occur at the orifice of a congenital hernia. The symptomatology of rupture of the diaphragm is much like that seen following any severe trauma to the abdomen. Shock is common, and severe. The patient will usually complain of extreme abdominal pain, and may even state that he feels as though his stomach were in his chest, or that he feels as though something inside of him had been torn. His face may bear the *riser sardonicus*. Respiration is usually rapid, shallow and painful. Deep inspira-

tion is impossible. Even after shock has disappeared the pulse will be very rapid. There may be painful, nonproductive cough. "Dry vomiting" is almost pathognomonic of the condition. There may be some rigidity of the abdominal wall on the side of the lesion. Unilateral thoracic immobility and bizarre physical findings at the lung bases are suggestive. In ruptures associated with lesions of the abdominal viscera or with fractured ribs the clinical picture may be most confusing. Wise practice urges that in all cases of contusion of the abdomen or thorax a roentgenographic examination be made. Simple fluoroscopy or anterior and lateral films are sufficient. Under no circumstances should bromum be given or any special procedures be indulged in. They are dangerous. Symptoms of old rupture of the diaphragm are essentially those of diaphragmatic hernia. The treatment of rupture of the diaphragm consists in waiting for shock to subside before attempting repair. Even though one must operate immediately to repair some other ruptured viscus the diaphragm should be left alone for a period of two to three weeks. Immediate phrenicotomy is of great value. This will put the involved side at rest, thus relieving much of the patient's painful symptoms and facilitating later operative procedures. The choice of approach is dictated by the individual case. Speed in operation is more important than a perfect repair. Fancy plastic operations are to be discouraged. The time required for them jeopardizes the patient's life. Anaesthesia is best administered by the positive pressure method. If this cannot be done it is advisable to do a preoperative pneumothorax.—*Les ruptures du diaphragme*, H. Constantin & M. Bonafos, *Arch Med Chir l'App Resp*, 1936, xi, 115—(C L D)

**Eventration of Diaphragm**—Although the term is a misnomer and is incorrectly used, it has come to mean a congenital or, occasionally, an acquired high position of one leaf of the diaphragm, characterized by aplasia or atrophy of the muscle fibres, with no break in the continuity of the muscle, and in most cases producing symptoms suggesting gastric, cardiac, pulmonary or pleuropulmonary origin. It should be distinguished from high diaphragm resulting from paralysis of the phrenic nerve. The condition appears to be congenital or acquired. In support of the congenital theory are the relative frequency on the left side (165 of 183 reported cases), frequency in the foetus, newborn and children, associated congenital anomalies, and absence of symptoms for a long time. For the theory of

acquired origin, the following causative factors have been given: trauma, acute infectious diseases, pulmonary tuberculosis, subphrenic abscess, mediastinal tumor, chronic gastric disturbances, nontraumatic lesions of the phrenic nerve, pregnancy, thoracic growths, aneurysm and subdiaphragmatic hydatid cyst. Pulmonary tuberculosis has been noted in a number of cases, but the exact relationship has not been definitely established. Only 4 cases in 16,504 roentgen examinations are mentioned at the Massachusetts General Hospital. It appears to be more frequent in males than females. The diaphragm, definitely elevated, may be a layer of fibrous tissue containing a few muscle fibres, or a thin aponeurotic sheet. The phrenic nerve on the affected side has been described as reduced in size but containing normal fibres. The lungs show no compression, but abnormally lobulated lungs are reported. The heart is usually displaced. A great variety of associated disease and congenital conditions are mentioned. Symptoms are varied, not characteristic and may be respiratory, gastrointestinal, circulatory and general. Thoracic and abdominal symptoms are most frequent. Typical but nonpathognomonic physical signs are mild or severe labored breathing, diminished tactile fremitus, displacement of the heart, and absence of the normal percussion note over the base of the lung on the affected side. There are no pathognomonic roentgen signs. A differential diagnosis must be made from hernia of the diaphragm, pleurisy with effusion, thickened pleura, intrathoracic stomach, pulmonary tumor, atelectasis, emphysema and neurosis. Prognosis is difficult and must be guarded, as far as life is concerned, it is usually good, but it is a disabling disease in many persons. Medical management is the treatment of choice and consists primarily of absence of physical exertion, hygienic and dietetic measures. Surgical intervention apparently offers little hope of cure. A review of eventration of the diaphragm has been given with the addition of two new cases.—*Eventration of the Diaphragm*, J. A. Reed & D. L. Borden, *Arch Surg*, July, 1935, xxxi, 30—(L F B)

**Fracture of Ribs From Coughing**—In a series of 1,903 tuberculosis patients admitted to the sanatorium over a five-year period, fracture of the ribs during the course of the pulmonary disease occurred in 30 patients, 23 women and 7 men, between the ages of 18 and 47. The fractures occurred in one or several of the ribs from the 5th to the 11th inclusive. In no instance were fractures of the upper 4 ribs found. The fractures were single in 17 instances and

multiple in thirteen, unilateral in 26 instances and bilateral in four. The highest number encountered in any one patient was four, the result probably of a series of accidents. The majority of the fractures occurred at approximately the junction of the anterior and middle thirds of the rib. Pain, though not severe, was an almost constant symptom and, like the characteristic pain of pleurisy, was aggravated on inspiration. The nature and location of the pain, and the absence, with few exceptions, of any displacement of the fragments on physical or radiographic examination, usually led to the erroneous diagnosis of pleurisy. In the cases cited, infection played no part in the causation of the fractures. It seems justifiable to assume that the fractures were brought about by muscular violence during coughing. The ribs are fractured more frequently than are the other bones of the body by muscular violence. The accident is not uncommon and occurs "especially in the consumptive," as stated by Stimson in 1883—*Indirect Fracture of the Rib in Pulmonary Tuberculosis*, E C Richardson, *J Am M Assn*, May 2, 1936, cv, 1543—(G L L)

**Early Diagnosis of Bronchiectasis**—In a series of 100 cases of bronchiectasis, 52 patients were males and 48 females. Seventy-seven were under 30 years of age at first observation. In forty-one the disease involved the left lung, in twenty-three the right lung, and in thirty-six it was bilateral. Fifty patients had symptoms of less than five years' duration, forty-seven of more than five years, and in three the duration was indeterminable. The onset is in early life. Seventeen patients whose ages varied from 4 years to 54 had had symptoms since infancy (17 per cent), 80 per cent dated symptoms from the first decade. In 45 patients onset was secondary to infection of the respiratory tract, in twelve it followed an infectious disease of childhood. The symptomatology and bacteriological observations are not distinctive. Of 66 patients in whom the accessory sinuses were examined roentgenographically, 86 per cent showed evidence of inflammatory change, in 24.2 per cent changes were marked. Roentgenographic and bronchoscopic examinations are essential for early diagnosis. Characteristic pneumonographic changes are necessary for indisputable proof of the existence of the disease. When direct roentgenographic examination is suggestive of bronchiectasis and the bronchoscopic and pneumonographic changes are indefinite, the patient should be kept under close observation and the examinations repeated—*The Importance of Early Diagnosis in*

*Bronchiectasis a Clinical and Roentgenologic Study of One Hundred Cases*, J T Farrell, Jr., *J Am M Assn*, January 11, 1936, cv, 92—(G L L)

**Serial Bronchography in Suppurative Pneumonitis**—The nasal fossa, pharynx, and larynx are anesthetized, and iodized oil passed through a rubber catheter under roentgenoscopic control. Using the selector, plates are taken at different intervals from the large bronchi to the pulmonary alveoli. In the acute stage of lung abscess the bronchograms show normal branches of a tree but no leaves. This is the picture in any acute pneumonopathy. When elimination begins the cavity with fluid level and the alteration of the draining bronchus may be seen. As the surrounding pneumonitis subsides, the roentgenographic tree acquires leaves. The dead-tree picture is produced by the iodized oil in the cylindrically dilated bronchi, but blocked from the small bronchi and alveoli. The bronchi may show cylindrical, ampullar, sacculiform or combinations of these dilatations. The bronchus draining the abscess may even be normal, but there is almost always bronchiectasis in the corresponding base. In a bronchiectatic abscess the roentgenogram usually shows a larger central cavity and smaller sacculiform cavities around it, while in suppurating bronchiectasis all the cavities are more uniform in size. Bronchial cancer may produce a large cavity which fills with the iodized oil but shows no bronchiectasis because there is no surrounding area of fibrosis. However, the carcinomatous cavity may not fill, but displace the whole bronchial tree at this level. Roentgenograms and bronchograms are given to illustrate these points—*Serial Bronchography in the Diagnosis of Suppurative Pulmonary Processes*, P L Farinas, *Am J Roentgenol & Rad Ther*, November, 1935, xxxiv, 579—(E M J)

**Progressive Idiopathic Pulmonary Fibrosis with Emphysema**—These cases, one of which is reported in some detail, are presented because often misinterpreted as pulmonary tuberculosis. Sometimes asthma, heart disease, malignant tumor and pneumoconiosis are confused. Unfortunately, even a complete pathological examination may not reveal the aetiology, but in general the necropsy findings are those of diffuse interstitial fibrosis, distortion and dilatation of bronchi, diffuse emphysema and, in advanced cases, emphysematous blebs. The X-ray picture is extraordinarily like that of pulmonary tuberculosis, but the disease is less localized. Emphysematous blebs may simulate cavities. Pleural thickening or ef-

fusion are common. A diffuse honey-combed appearance is produced by the thin-walled dilated bronchi and confluent emphysematous alveoli. Cavities, when they occur, are multiple and molded to one another. They may be best seen on oblique or lateral view. Diaphragmatic outlines and excursions are usually abnormal. The condition is progressive and shadows do not clear or disappear as in tuberculosis.—*Progressive Idiopathic Pulmonary Fibrosis Associated with Emphysema*, A. O. Hamplor, Meeting Mass. Med. Soc., June 5, 1935, reported in *New England J. M.*, December 12, 1935, ccciii, 1174—(A P)

**Massive Collapse Complicating Haemoptysis**—A lad of 18 was admitted, October, 1934, to Westminster Hospital, London, with a history of initial haemoptysis in August. Atelectasis apparently developed during and following repeated further haemoptyses, and involved the left lung. It persisted several weeks and gradually disappeared. Physical and X-ray examinations and bronchoscopy were negative. Definite symptoms of pulmonary tuberculosis recurred early in 1935, with positive sputum, and sanatorium treatment and artificial pneumothorax were carried out. Massive collapse after haemoptysis is infrequently diagnosed, although it is probably not uncommon. Such patients are mostly too ill to be subjected to exhaustive clinical and roentgenographic examination, and some of the manifestations are mistaken for changes due to old fibroid tuberculosis. Most authors assign mechanical bronchial occlusion by a blood-clot as the causative factor, a view supported by the fact that reinflation of the collapsed lung does not occur until the offending clots are expelled. Benedetti, however, believes that all varieties of massive collapse are due essentially to active contraction of lung tissues, especially the smooth muscle of the respiratory bronchioles, from reflex nervous stimulation, and that, following bronchial spasm, there is progressive absorption of alveolar air. Most cases occur in patients with early pulmonary lesions. The observations of Jacobaeus and Westermarck are confirmatory. In most of their cases haemorrhage was large and in many it was an initial symptom of tuberculosis. Jacobaeus showed that spasm occurred particularly in patients with healthy bronchi. Lipiodol rarely induced collapse in diseased lungs, but in three of eight healthy individuals massive collapse ensued. With complete mechanical obstruction alone, collapse did not occur for four to six hours. Most reported cases (following haemoptysis) have occurred in young adults, more often

men, pulmonary tuberculosis being the chief causative agent. A few have been reported associated with such other conditions as mitral stenosis, vascular hypertension, and bronchial tumor (Morlock and Pinchin), also "idiopathic" haemoptysis during menstruation in young girls. The areas of collapse vary greatly in size and location. The symptoms are often masked by those of the haemorrhage, develop within twenty-four hours, and resemble those of postoperative collapse. Dyspnoea, cyanosis, and chest pain are common. Flattening and diminished movement of one side are usual, and either diminished, absent or tubular breathing, also, displacement of heart and trachea toward the affected side. The X-ray picture is characteristic, with a dense homogeneous opacity, narrowing of the hemithorax and intercostal spaces and increased obliquity of the ribs, also elevation of the diaphragm and mediastinal displacement, homolateral. When therapeutic pneumothorax is attempted, Jacobaeus and others have found unduly marked negative intrapleural pressures (−30 to −40 cm. water). In most cases the cause of the haemoptysis has been revealed with the disappearance of the X-ray shadow of atelectatic lung. Recollapse is usually complete and the immediate prognosis good. Artificial pneumothorax has been recommended by Jacobaeus, Wilson, Glenn and others, it usually relieves the acute symptoms and favorably affects the tuberculosis. In diagnosis, the condition must be differentiated from bronchopneumonia, which carries a bad prognosis. In pulmonary tuberculosis there may occur a chronic as well as acute collapse of a lobe or lung, due to bronchial stenosis. This must be differentiated from pulmonary fibrosis. The best method of distinction is by inducing artificial pneumothorax, the characteristic high negative pressure being registered with atelectasis. The possibility of a bronchial neoplasm as a factor may have to be ruled out by bronchoscopy. In this paper, 41 cases collected from the literature are tabulated in some detail.—*Massive Collapse of the Lung Complicating Haemoptysis*, J. Mindline, *Brit. M. J.*, December 21, 1935, no 3911, 1201—(A P)

**Bilateral Spontaneous Pneumothorax**—The course of a case with an idiopathic spontaneous bilateral pneumothorax is discussed. From a consideration of the nature of the air-vesicles, it was probably a case of acquired bronchiectasis, foetal bronchiectasis, or congenital cystic lung, and of these the latter seemed the most probable. The pneumothorax probably oc-

curred through the rupture of some of the emphysematous vesicles, which were in communication with the bronchial system — *A Case of Bilateral Spontaneous Pneumothorax, Probably Caused by Rupture of Air Vesicles in the Lungs*, B-E Walinder, *Acta Tuberc Scand*, 1936, x, 66 —(I B S)

**Interlobar Pleural Effusions**—Encapsulated pleural effusions in the costophrenic angles, the anterior and posterior mediastinal aspects of the pleurae, the retrocardiac area, and the interlobar fissures (including the arigos fissure on the right side) may be difficult to detect on physical and the usual roentgenographic examination. They may account for so-called mild and atypical pneumonic processes, unresolved pneumonias, and some intrathoracic neoplasms which disappear miraculously. In interlobar pleurisy there are slight chills and moderate amount of fever, constant dull chest pain not particularly aggravated by the respiratory effort, a distressing cough but no bloody sputum. The symptoms may be even more mild and, if occurring in a patient past middle age, are likely to be considered as due to neoplasm. The roentgenological evidence may be that of pulmonary consolidation, but physical signs are absent or limited to harsh breathing and, rarely, small moist râles. In interlobar pleurisy the roentgenological findings persist longer, the leucocytosis and preponderance of neutrophils is less marked, and there is not the sharp drop in temperature seen in lobar pneumonia. The best diagnostic evidence is a roentgenogram, showing the interlobar fissure at right angles to the film and with the involved side next to the film. The right upper interlobar septum is often demonstrated in routine roentgenograms since the anterior aspect of the fissure is at right angles to the film. Although this is true, the right lateral position is best for showing effusions in even this fissure. Rare neoplasms, arising in the parenchyma and growing in globular fashion near the centre of the lobe or originating in the hilar structures and growing outward, may be confused with interlobar effusion. If lateral films show these supposed tumor shadows to be intimately connected with an interlobar fissure, time and patience may prove them to be effusions which slowly but surely disappear. Case histories and roentgenograms are given—*Interlobar Pleural Effusions*, B P Strelman, *Am J Roentgenol & Rad Ther*, October, 1935, xxxiv, 475 —(E M J)

**Acute Empyema**—Experimental studies and clinical observation on acute empyema with suggestions as to methods of treat-

ment are presented. Reexpansion of the lung on the affected side was delayed or prescribed by thickened pleura, and in the experimental work it was found in some cases that a pressure sufficient to rupture the alveoli did not reexpand the lung. It was noted in the acute stage that hyperplasia of the subpleural alveolar epithelium occurred. This is described as part of the pathology of certain diseases of the lungs, and observations in one human case indicates that it may occur with this type of empyema. These observations supply further evidence that the alveolus of the lung is actually lined with epithelium—*Acute Empyema Thoracis*, H A Carlson, *J Thorac Surg*, April, 1936, v, 393 —(L F B)

**Oil in Lung**—Three adult cases are reported, in which pulmonary changes occurred, following the prolonged or intensive use of mineral oil in the respiratory tract. In all of these cases oil droplets were constantly found in the sputum. Unusual X-ray findings were noted. There was a milky mottling in the areas involved. On close examination, this was found to be due to accentuation of the finer lung markings. Serial films showed definite progressive restriction in the size of the lobes involved with solidification where the involvement was most severe. Accompanying this is a compensatory emphysema of the upper lobes. Generally the lung fields nearest the cardiohepatic angle show the greatest density. In a case which came to autopsy, oil droplets were visible on the cut surface of the fibrotic lung, the last instillation in this case occurring over six years before. Attention is called to the fact that the vegetable oils produce little reaction in the lung—*Roentgenographic Changes Following the Introduction of Mineral Oil in the Lung*, K S Davis, *Radiol*, February, 1936, xxvi, 131 —(G F M)

**X-Ray Changes in Lungs of Electric Arc Welders**—Among 16 electric arc welders, all apparently healthy and actively working, and nearly all young men, apprenticed at 14, the X-ray films of six showed a diffuse generalized mottling throughout the lung fields, and none appeared entirely normal. Some of the definitely positive cases showed crepitations at the lung bases on physical examination. Three cases classified as "suspicious" showed some nodular stippling and exaggerated markings in the films and even a suggestion of mottling in one. The "negative" ones showed slight stippling in certain areas and abnormally prominent markings. None showed abnor-



real physical signs. The diagnosis of the underlying pulmonary lesions in these cases is important but highly speculative. There is little doubt that the dust or fumes inhaled played an etiopathological rôle. During welding operations, dense white or grayish white fumes rise continuously and, in the absence of protective measures, large quantities can not fail to be inhaled. The electrodes or welding rods, containing a metallic core and an outer covering, are gradually consumed by the heat generated. The metal of the core becomes molten and assisted by the flux of the covering, spreads over the surface of the metal welded. The basis of most of the coverings is sodium silicate, some containing asbestos, which sometimes completely covers the rods, and at others is wound spirally. The composition of the fumes has yet to be fully investigated. The particulate matter, collected in an Owen dust-counter, consisted in one instance of iron-oxide particles and occasional asbestos fibres. The X-ray appearance is not that of asbestosis. In only one instance was the diaphragmatic or cardiac outline blurred or the line of the interlobar septum seen. The upper lung fields appear more affected than the lower. Generally, the appearance is more suggestive of silicosis, but the men present no symptoms or incapacity for work, with one exception, none are dyspnoeic, and none have pulmonary tuberculosis. It is suggested that nitrous fumes, together with fine iron-oxide dust, may set up small areas of chronic inflammation, congestion or fibrosis in the lungs, or even that the particulate particles may be visualized by the X-rays—*X-ray Appearance of the Lungs of Electric Arc Welders*, A. T. Doig & A. I. G. McLaughlin, *Lancet*, April 4, 1936, ccxxx, 771—(A. P.)

**Roentgenology of Pneumonoconiosis**  
—The antemortem and postmortem roentgenograms are correlated with the pathological changes in various unclassified types of pneumonoconiosis. To facilitate this attempt, the field of pneumonoconiosis is divided into a convenient and logical working classification, based chiefly on the type of pathological change, combined with the causative agent. Four main divisions are listed as follows: (1) coniofibrosis, including silicosis, silicotuberculosis, asbestosis and the like, (2) coniolymphostasis, including anthracosis, siderosis and the like, (3) coniotoxocosis, including protein sensitization, direct irritation and other causes, and (4) mixed processes, such as anthracosilicosis, siderosilicosis, anthracosilicotuberculosis and other conditions. Coniofibrosis may be considered as a form of pneumonoconiosis charac-

terized by an exuberant growth of connective tissue due to a specific irritant. In silicosis the action is viewed as that of a toxic irritant. Whether it is a direct poison acting on the cells or an indirect one due to the solubility of the silica has not been established. Whorls of fibrous tissue develop. The stage of the disease depends on the location and number of these nodules. After the entrance of the tubercle bacillus into a silicotic process, the character of the silicotic nodule changes depending on the time of appearance of the infection and the dosage of bacilli. The longer the tuberculosis exists as a widespread process, the fibrils of the whorls become blended into one mass, and the whole nodule gradually takes on the appearance of a caseous nodular tubercle. As the process advances, it becomes more and more like a tuberculosis, until the roentgenograms are typical of this disease. If there is a benign tuberculosis already present, the process tends to become more exaggerated in the regions of the tuberculous lesions. In addition to the variations in the lung parenchyma, there are changes in the lymph nodes that are characteristic. Here there is an "egg shell" infiltration of calcium underneath the capsule. The pathological disorder in asbestosis is not a nodule as in silicosis but rather a diffuse fibrous lobulitis. The process extends out from the hilum toward the base. While asbestosis is not so prone to become tuberculous as silicosis, it does possess this hazard. The second main group, coniolymphostasis, includes only dusts that act principally by blocking the lymphatics until their normal physiological function is so impaired that normal resilience is lost, lymph-drainage is impaired, and acute infections readily occur. In the pure inert dusts there is rarely any fibrosis, especially nodules or whorls. In the worst types the lymphatics are completely blocked and are essentially functionless. The third group, coniotoxocosis, is somewhat apart from the other types in that the irritants affect the tissues directly or after a period of sensitization to a specific protein. Most of these are acute processes such as a bronchitis or a pneumonitis. The shadows reveal a distribution similar to uncomplicated silicosis, but the lesions are soft and irregular and conform to the acini similar to an acute bronchogenic spread of tuberculosis. As illustrative of the fourth group, in most coal miners there is a mixed process that has been termed anthracosilicosis. In general, there is a rapid accumulation of carbon with a gradual development of silicosis, which seems to be greatly retarded by the coal-dust. The roentgenogram shows first an increase in the thickness of the hilum lymph nodes and

of the peribronchial and plevascular lymphatics due to the dust. Later, nodules begin to appear which vary in size from a few millimetres to many centimetres. The inert dust seems to alter the circulation in the tissues, so that a partial atelectasis results, to be followed by fibrosis, resulting in fibrous tumor, composed of fibrous tissue with phagocytes laden with dust in between the fibres. In the ordinary coal miner with low silica the terminal condition is usually bronchitis or pneumonia, but in the lead- and zinc-miners of the Ozarks, where the carbon pigment in the quartz is low compared to the silica, the result is a moderate anthracosis with a strong silicotic tendency. Sooner or later they are usually contaminated with the tubercle bacillus—*Pathologic Interpretations of Roentgerologic Shadows in Pneumoconiosis*, H C Sueany, *J Am M Assn*, June 6, 1936, cvi, 1959—(G L L)

**Asbestosis**—Asbestosis is distinct from silicosis in its pathology and clinical features. A search of all the death-records on file in the Metropolitan Life Insurance Company revealed that asbestosis had been given as a cause or contributing cause of death in only 19 cases, fifteen of which have occurred since 1933. The clinical picture of asbestosis is milder than that of silicosis. The author did not find in communities in which asbestos was mined or fabricated the familiar picture of disability and tuberculous infection so characteristic of hard rock mining communities. In only one case was there evidence of active tuberculosis, as based on the roentgenography. Several showed healed tuberculosis. The author's data are based on 126 physical examinations of asbestos workers, all of whom had more than three years' exposure and were selected at random. Sixty-three of these presented roentgenograms thought to indicate pneumoconiosis, but the symptoms were indefinite and inconclusive. These cases were called first-stage. Four presenting evident pulmonary symptoms and corroborative roentgenograms were termed second stage. Of these 67 patients, twenty had been exposed more than ten years, and thirteen more than fifteen years. As in silicosis, the diagnosis centres on the roentgenogram. The X-ray appearances are not clear-cut or distinctive, as in silicosis, and do not lend themselves to ready grouping into progressive stages. There are less evident pathological changes, and the shadows are finer, more granular, and softer than in silicosis. The asbestosis film gives the impression of ground glass, and there is no nodulation with the consequent tendency of the nodules to coalesce and give dense opaque areas in the films. The

distribution of the shadows is somewhat different, occupying the lower third of the lung, except in far advanced cases, when the shadows may occupy the major portion of the lung. The exact significance of asbestos bodies in the sputum is doubtful, but it is commonly agreed at the present time that they are not diagnostic of pulmonary fibrosis and indicate merely that the individual has been exposed to asbestos dust. It is not certain that asbestosis progresses as does silicosis after withdrawal from dust exposure, nor does infection seem to be as closely and intimately associated with asbestosis as with silicosis—*Asbestosis*, A J Lanza, *J Am M Assn*, February 1, 1936, cvi, 368—(G L L)

**Tissue Changes from Colloidal Sillicic Acid**—Maximum tissue changes in a silicotic lung do not occur at the sites where relatively large particles of quartz can be demonstrated. This may be due to the passing of the quartz crystals into a colloidal state, which can occur only in a slightly alkaline medium, and then, on reaching a slightly acid medium, the crystalline state returns. On the other hand, the tissue juices may digest the quartz into finer particles by a sort of corrosive process. The author believes that both processes may occur. Assuming that the changes found in a silicotic lung were on a physicochemical rather than mechanical basis, the author injected rabbits intravenously with a pure, stable, water-clear preparation, completely electrolyte free, containing 0.25 gm of silicic acid per 100 cc. The rabbits received 1 cc daily, and, in later experiments, 2 cc. Those receiving 2.5 mgm daily for six, eight and twelve weeks were killed at the end of these various periods of time. They were all found to have enlarged spleens and livers, those receiving the most silicic acid having the largest, which were of very tough consistency. Microscopic findings in the liver of an animal treated for six weeks were significant. There was a marked increase in interstitial tissue, with swelling of the walls of the bile capillaries, and decrease in the size of the liver cells, which often made it difficult to differentiate them from the interstitial and capillary-wall cells. Between the endothelium of the capillary walls and the liver cells proper were spaces lightly streaked or completely filled with a homogeneous substance which stained red with eosin. Generally this appearance was accompanied by a marked increase in the cellular elements. The Kupffer cells were increased in number and size, and appeared as large, finely vacuolated cells, rich in protoplasm. These changes were most marked

near the central vein. In certain regions there was no evidence of pericapillary oedema, but the endothelial elements were swollen and increased in number, and occasionally sinus-like outpouchings of the capillary walls were present. The pericapillary areas noted above stained red with Van Gieson's stain, but without evidence of collagenous fibrils. The liver of a rabbit treated for eight weeks showed all the above changes. In addition to these, young connective-tissue cells were so abundant that the structure of the liver was in places difficult to make out. A development of collagenous fibres had taken place, and the parenchyma was much reduced in amount. What remained stained poorly and tended to blend with the collagen. In the rabbits treated for twelve weeks the process had gone still further, and took on the appearance of cirrhosis of the liver. There was no evidence of cellular inflammation, however, nor any hyperplasia of bile-ducts. Connective tissue had replaced the liver cells. There was still an extensive pericapillary oedema, with a tendency to collagen formation, and an exudate containing a fine fibrillar network lying between the capillary walls and the liver cells. Studies of the spleens from these animals revealed similar changes. There was an increase in the reticulum of the pulp cells, which were unusually rich in protoplasm. The nuclei were often eccentric and irregular in shape. The protoplasm was very light and transparent, and finely and coarsely honeycombed. Swelling and mobilization of the pulp cells, morphologically equivalent to the changes observed in the Kupffer cells of the liver, was present. In those animals treated for twelve weeks there was a significant fibrosis of the reticulum with a tendency to collagen impregnation of the fibrils. There were no changes of note in the lymph follicles of the spleen, but striking changes in the glomerules of the kidneys. In animals treated for only eight weeks there was a high grade intracapillary glomerulitis, with proliferation of the endothelial elements. The nuclei of these cells were lighter in color than normal and frequently lay at the side of the cell. The protoplasm was light, and contained large vacuoles. At the periphery of the glomerules were collagenous fibres. There was a marked excretion of albumin. In the bone marrow was a marked oedema, retrogression of the blood-forming elements, and an increase in number and impregnation with collagen of the reticulum fibres. In the lungs there was a slight increase in the supporting structure of the alveolar walls, due to an increase in the number of collagen fibres. In general, there was a mobilization of the endothelial elements, and a high-

grade protein rich pericapillary oedema and exudate. These would lead to a reduction in the parenchymal elements, and a development of sclerosing connective tissue. In silicosis and asbestosis the process of fibrosis is bound up with the presence of colloidal silicic acid, which is a normal and necessary constituent of collagen. Indeed, all of the silicate which the body can change to silicic acid must be utilized to build new connective tissue. This silicic acid is negatively charged, for positively charged colloidal split-products of silicates, such as are present in clay, will not lead to sclerotic changes, and are harmless. That the pathological picture of asbestosis differs somewhat from that of silicosis is explained by the fact that, in the former, silicate is present as fine needle-like crystals which stay where they have originally lodged, thus permitting the dissolved silicic acid to diffuse freely into the tissues. Hence, there is no such high local concentration of the material as there is in and about the lymphatics in silicosis where the fine particles of quartz are readily carried to and block the lymph nodes—*Untersuchungen zur Pathogenese silikotischer Gewebsveränderungen*, F. Köppenhofer, *Iserschow's Arch.*, June 18, 1936, cccxvii, 271—(C L D)

**Squamous-Cell Cancer of Lung with Asbestosis**—If cancer is to be adjudged as of industrial origin, its incidence in a particular occupation should significantly exceed the general rate, and there should be sufficient association of the worker with a substance proved experimentally to be carcinogenic. The liability of malignant tumor to supervene upon long standing pneumoconiosis has been suggested but their precise interrelation is an open question. Two cases are recorded, in women workers, one after eight years' exposure to asbestos dust as a spinner the other occurred fifteen years after two short periods of six and thirteen months in the mattress and opening departments of the factory. The malignant lesions in each case were small and not recognized during life. In each case, the asbestosis was advanced and of long standing, and the growths were small and circumscribed and with no metastases. They were in a portion of the lung in which asbestosis was advanced. Neither growth nor asbestosis seemed sufficient to have caused death but it is suggested that in asbestosis a small tumor turns the scale—*Two Cases of Squamous Carcinoma of the Lung Occurring in Asbestosis*, S. R. Gloyne, *Tubercle*, October, 1935, xvii, 5—(A P)

**Primary Cancer of Lung**—Primary carcinoma of the lung is one of the most

frequent forms of malignant tumor in adults. The authors have studied 135 cases over a four-year period. Their statistics indicate that it ranks second to gastrointestinal cancer, and constitutes from 6 to 8 per cent of all malignant tumors. About 75 per cent of the cases occur between ages 40 and 60 years. In the series of 135 cases it was twelve times as frequent in males as in females. The right upper lobe is the most common site. The tumors are all bronchogenic in origin, and begin as a metaplasia of the bronchial epithelial cells. There are three important histological types: (1) undifferentiated round or spindle cell, (2) adenocarcinoma and (3) squamous cell. All types have a marked tendency to produce lymphogenic and haematogenic metastases, but the squamous cell is usually less malignant than the other two types. Of 74 cases that came to necropsy only one presented no metastases. Eighty-eight per cent showed hilar lymph node metastases, 38 per cent abdominal lymph node, 40 per cent liver, 32 per cent kidney, 43 per cent suprarenal, 28 per cent bone, and 24 per cent brain metastases. The chief associated lung changes were pleural effusion (47 per cent), bronchiectasis (43 per cent), acute pneumonia (28 per cent), chronic pneumonia (20 per cent), abscess or gangrene (20 per cent), and purulent bronchitis (19 per cent). Only 49 per cent of cases presented changes that were largely thoracic. This important fact explains the present failure in most clinics to diagnose 50 per cent of the cases. The characteristic history of pulmonary well being to within an average period of eight months before seeking medical aid, the development of bronchitis or recurrent attacks of pneumonia or pleurisy, followed by persistent cough, pulmonary or extrapulmonary pain, haemoptysis, and dyspnoea, should enable the physician to suspect lung carcinoma. The roentgen study alone makes the diagnosis possible in at least two thirds of the cases. The bronchoscope is of great value in confirming the diagnosis, but most cases can be recognized without it.—*Primary Carcinoma of the Lung: A Diagnostic Study of One Hundred and Thirty-five Cases in Four Years*, A. Arkin & D. H. Wagner, *J. Am. M. Assn.*, February 22, 1936, *vol.* 587—(G. L. L.)

**Early Diagnosis and Treatment of Cancer of Lung**—The surgical treatment of malignant disease has been based on the complete extirpation of cancer-bearing tissue or of a cancerous organ prior to metastasis and the success of such treatment depends upon early diagnosis and accessibility. It has been demonstrated that either one lobe of a lung or the entire lung

on one side can be successfully removed without limitation of the patient's life or activities. Recent advances in such surgical treatment demand that the general medical profession be more concerned with early symptoms and differential diagnosis. In most cases a warning symptom, a persistent cough, appears early, also, most growths originate in a stem-bronchus and can be actually visualized bronchoscopically. Surgery is the more to be considered inasmuch as irradiation in any form fails to cure and often has no favorable influence whatever on these lesions. As the most common type of primary lung tumor is the epidermoid, notably radio resistant, and sometimes even aggravated or broken down, not much reliance can be placed in such therapy. Bronchoscopic removal is applicable only to very small localized lesions. Efforts at surgical removal have been stimulated by successful experiences with lobectomy for bronchiectasis, notably by Sauerbruch, Churchill, Edwards and Eggers, in the case of a single lobe, and by Nissen, Haight, Windsberg, Graham and Singer, and Rienhoff, in the case of the entire lung, in both bronchiectasis and carcinoma. **Pathology** Most primary lung tumors are conceded to arise from bronchial epithelium or mucous glands, and the epidermoid form is most frequent. Most writers distinguish two major groups according to location: (1) hilar and (2) peripheral or pneumonic. The latter are more frequently adenocarcinoma. Most epidermoid tumors eventually show mediastinal extension. The majority of tumors originate in a main stem bronchus near the hilum (65 to 75 per cent). In the earlier stages these often give rise to a mistaken diagnosis of asthma. When they completely occlude a bronchus there is atelectasis, showing a homogeneous triangular shadow on X-ray. **Symptoms and diagnosis** In a review of the earliest symptoms in 19 cases of bronchogenic carcinoma, cough was reported by all to be an early and persistent symptom, while 12 patients complained of weakness and 8 of haemoptysis. Roentgenographic examination in the early stages may be confusing in that the lesion itself may cast no shadow or one difficult of interpretation because of its close proximity to the hilum. Most abnormal shadows seen on X-ray are due to the secondary effect of the tumor rather than the tumor itself, as, for instance, atelectasis of a lobe. Sputum examination helps to rule out tuberculosis and differentiate lung abscess. Bronchoscopic examination is very important. There is a pneumonic form, showing an area of density with central necrosis, fairly well circumscribed, often progressing to cavitation, with evi-

dence of sepsis. Edwards has reported that 10 per cent of cases diagnosed as pulmonary abscess prove to be broken down neoplasms. In this type bronchoscopic examination is of least assistance. The history and serial X-rays are most suggestive. Among other aids to diagnosis generally are lipiodol and partial artificial pneumothorax. *Operative therapy.* The advisability of this must be determined on the basis of extent of the lesion and the general condition. Preliminary pneumothorax is generally advised, to be maintained seven to ten days. If, on exploration, there are obvious metastases, the operation is not continued.—*Primary Carcinoma of the Lung. Early Diagnosis and Treatment by Pneumonectomy*, R. H. Overholt, *New England J. M.*, January 16, 1936, *ccxvii*, 93—(A. P.)

**Diagnosis of Bronchial Cancer.**—A group of 50 cases of bronchial carcinoma were studied from a diagnostic standpoint. Each case was based on histological examination of the tumor tissue. Forty-five of the patients were males, the ages ranged from 21 to 69 years, the greatest proportion occurring between 41 to 60 years of age. The symptoms most frequently complained of were cough, expectoration, pain, dyspnoea, loss of weight and haemoptysis, in the order named. Fever, haemorrhage, dysphagia, and vague respiratory diseases were also noted as initial symptoms. Cough was present in all cases but one, and was the first symptom in over half of the cases, occurring alone or with some other symptom. It was endured for a relatively long time after the onset before medical aid was sought. Pain was tolerated for a shorter time before advice was sought. In over half of the cases the initial symptom had been present for a year before a physician was consulted, and only 25 per cent were seen within six months from the time of onset of initial symptom. The most common roentgenologic finding in bronchial carcinoma is evidence of atelectasis. This is due to obstruction by the tumor, which, like any foreign body, may produce a check-valve or stop-valve type of action. At first, neoplasms probably have a check-valve action, but symptoms produced from this may not be severe. Adults do not seem to suffer greatly from this type of occlusion; only one patient in this series was seen at this stage. Forty per cent of the cases had complete collapse of a lung or part of a lung when first seen. A mass seen in the parenchyma of the lung generally means a new growth, but the exact nature of the tumor cannot be determined from the roentgenogram. If such a mass is near the hilum it may be hard to differentiate from

an aneurysm. Such an X-ray finding was present in 24 per cent of these cases. An increase in the pulmonary markings resembling an inflammatory change is an atypical finding in some cases of bronchial tumor. Such findings may be interpreted in the upper lung field as tuberculosis and in the lower as bronchiectasis. Any shift of the mediastinum with such findings should make one suspicious of a new growth. In a few cases there is roentgenological evidence of pulmonary abscess. When it occurs secondary to bronchial carcinoma, there is frequently some displacement of the viscera, which does not usually occur in abscesses secondary to operation or infection.—*Diagnosis of Bronchial Carcinoma. A Clinical and Roentgenologic Study of 50 Cases*, J. T. Farrell, *Radiol.*, March, 1936, *xxi*, 261—(G. F. M.)

**Removal of Intrathoracic Dermoid Cyst.**—A patient, admitted to Victoria Park Hospital, London, complained of cough with sputum, having been referred from a dispensary and sanatorium, where a chest X-ray revealed a shadow suggesting tumor. She also had had a complicating miscarriage in the 6th month of pregnancy, immediately prior to admission. The X-ray film showed an oval shadow on the right side contiguous with the mediastinal shadow, from the 2nd rib above to the lower border of the fifth below, with maximum convexity in the mid-clavicular line. Laterally viewed, it appeared to be anterior. The fluoroscope showed no pulsation, and further X-ray after lipiodol showed no bronchial distortion or compression. Dermoid cyst was diagnosed, and exploratory thoracotomy recommended. However, a preliminary artificial pneumothorax was induced. At operation an oval mass was discovered contiguous with the mediastinum and anterior to the collapsed lung, of hard consistence, but containing cloudy fluid. It was dissected off the lung superior vena cava and pericardium, and removed, the wound being closed. Recovery was uneventful except for a blood-stained effusion in the pleura necessitating aspiration on the 3rd and 5th days. The walls of the cyst contained muscle tissue, and the interior numerous thin plates of bone, as described by Gloyne. *Discussion.* Tumors, limited to the mediastinum when first discovered, are rare, and a diagnosis of their nature usually difficult. However, a malignant growth of the size of the tumor noted is usually associated with more evidence of ill health and a grayish color is suggestive. Restoration of health following a holiday speaks against malignant tumor. Aortic aneurysm may closely simulate mediastinal tumor due to other cause, and absence of

pulsation is not conclusive, nor is even exploration in certain cases. Next to malignant tumor and aneurysm, a dermoid cyst should be considered, especially if the location is anterior. Neurofibroma is usually situated posteriorly, and lymphadenoma limited to the hemithorax, if it occurs, must be very rare. Operation in the case of a dermoid cyst will prevent further growth and complications.—*An Example of Intra-Thoracic Dermoid Cyst*, H. B. Wood, *Tubercle*, Mar., 1936, xii, 364—(1 P)

**Cystic Disease of Lung**—Eight cases of cystic disease of the lung illustrative of three types of this condition are reported. In case 1 the condition had manifested itself clinically only by infrequent haemoptysis over a period of twenty nine years. Physical examination of the chest was negative, and the history and roentgenogram gave no evidence of an inflammatory process. There were present several circular and oval cysts bilaterally in the lower lobe of each lung. The largest was 6.5 cm. in diameter, and was filled with fluid blood which was spontaneously evacuated. Because the health of the patient was not impaired, and because there was no recurrence of haemoptysis during the period of observation, pneumothorax was not induced even though it might have led to permanent collapse of the cavity. In case 2 there had been no symptoms until the patient, a woman, was eighteen years old, when she suffered a peculiar "pneumonia" which lasted two weeks, but was without sequelae. Three years later, at three days postpartum, she had a sudden severe pain in the right chest associated with moderate dyspnoea. No other symptoms were present, and the pain and dyspnoea disappeared in twenty-four hours. A roentgenogram was interpreted as showing spontaneous pneumothorax on the right side, and the patient took a ten months' cure for tuberculosis. A few months later she began having infrequent episodes of pain in the right side of her chest with dyspnoea. This persisted for one year when she was admitted to the hospital for study. Physical examination revealed hyperresonance, and diminution of breath sounds over the entire right lung. The heart and mediastinal structures were displaced moderately to the left. The left lung was clear. A roentgenogram showed an air space in the right apex, below which were numerous air-cysts, some of which were several inches in diameter. Manometric readings showed negative pressure in the apical air-space, which was probably a localized pneumothorax produced by a ruptured air-cyst. The shift of the mediastinum to the left had been produced

by pressure of the previously distended air-cysts with atmospheric or even positive pressure. The pressure in the pneumothorax sealed off the opening and the air was gradually absorbed. The resulting decreased intrapleural pressure permitted spontaneous rupture of adjacent air cysts into it. This would explain the recurrent pain and dyspnoea. The patient's symptoms did not seem to be severe enough to warrant the injection of iodized poppy seed oil with the idea of producing an inflammatory reaction which would be followed by closure of the cyst. This has been successfully accomplished by Crosswell and King. Three more cases of cystic disease of the lung are described, in which there was extensive pulmonary fibrosis, which had presumably preceded the development of the cysts. These patients were all over forty years in age. The cysts developed from emphysematous blebs formed in the neighborhood of the fibrosis. These cysts were of the bullous type. One patient, case 3, complained of slight productive cough and dyspnoea. Roentgenogram revealed diffuse fibrosis of both lungs and a dense shadow at the root of the right lung. There was nothing to suggest the numerous large thin-walled cysts seen in this lung at autopsy. The patient died of a cerebral accident. The left lung contained no cysts, but showed a tendency to the formation of bullae. Case 4 was that of a person who complained only of a recent haemoptysis and pain in the right side. A diminution of breath sounds and fine moist râles were present at the right base. X-ray revealed bilateral diffuse fibrosis, and a large bullous cyst in the right lower lobe. Case 5 was one of polycythaemia without pulmonary symptoms. A routine roentgenogram of the chest showed a large air cyst in the right apex and adjacent to an area of fibrosis. In cases 6, 7 and 8 there had been bronchiectasis and chronic pneumonitis of many years' duration. One case had a transient anaerobic infection in a cyst. Another had a small area of healed tuberculosis in the right lung, with cysts present only in the left. This was confirmed at autopsy. The patient died of erysipelas. The right lung was a fibrous mass, containing innumerable cyst-like cavities communicating with dilated bronchi. There are two main types of air-cysts, those that originate from dilated bronchi and whose walls contain muscle fibres or cartilage, and those which are essentially emphysematous blebs. They may be solitary or multiple. The solitary cysts are rare and are encountered usually in infancy. They are large and are usually fatal in early life. They will rapidly increase in size if there is established a

check-valve type of bronchial opening. Their sudden rupture results in a tension pneumothorax that may end fatally. Multiple cysts vary in size, distribution, type of bronchial communication and contents. They may be congenital or acquired, a distinction which is often difficult to make in adults. Pneumonitis and fibrosis are invariably associated with the acquired form—*Cystic Disease of the Lung, H. Hemmell, Arch. Int. Med., January, 1936, lxxi, 1—(C. L. D.)*

**Congenital Cystic Lung**—One hundred and forty seven of these cases have been reported in the literature to date, most of them being of the large solitary type of cyst in which the age of onset is earlier and the prognosis very poor. Symptoms are severe, and recognition is usually easy. Recurrent attacks of dyspnoea and cyanosis in an infant with hyperresonance and mediastinal displacement should suggest a cyst rapidly filling with air. Roentgenograms, either alone or with lipiodol, should confirm the diagnosis. Small multiple cysts may remain silent unless infection supervenes. Unfortunately, infection is the rule. Symptoms simulate severe bronchiectasis and death usually occurs within the first few weeks or months of life. The particular case reported is interesting because of its duration. A girl, three and one-half years old, first came under observation because of an ulcerated phlyctenular conjunctivitis. The tuberculin test was strongly positive. She gave a history of nonproductive, spasmodic cough, which was severe enough in the first four months of life to be considered whooping-cough. Many fine crackling râles were heard over the left base posteriorly, and the roentgenogram showed a triangular area of honey-combed, increased density in the right cardiophrenic angle. The lateral line was quite sharp and straight, and ended at a point on the diaphragm where there was tenting. Both hilum shadows were a little heavier and considerably more extensive than normal. The heart and great vessel shadow was within normal limits. A diagnosis of bronchiectasis was made although tuberculosis was suspected. When next seen, ten years later, she still had cough (nonproductive except when she had an occasional cold) and was underweight but had no cyanosis, clubbing of the nails and no dyspnoea on playing games at school. Examination revealed only slight lagging of the right side on inspiration and harsh, high pitched breath sounds over the right lower chest anteriorly. Roentgenography revealed the same straight diagonal line, tenting of the diaphragm and cysts, whose

walls were thinner, showing no infection now. A diagnosis of congenital cystic formation in an accessory lobe of the right lung was made. The two anomalies were interrelated, one probably causing the other. The straight lateral line is found in accessory lobes, while a concave line is found in an atelectatic lobe, the lower line of which flattens out along the medial portion of the diaphragm. This accessory lobe being surrounded by normal lung tissue accounts for the paucity of physical findings and the smallness of the involved area partially accounts for the favorable outcome—*Congenital Cystic Lung. A Report of Multiple Cysts in an Accessory Lobe, M. J. Thorpe, Am. J. Roentgenol. & Rad. Ther., December, 1935, xxvii, 724—(E. M. J.)*

**Syphilis of Lung**—Syphilis of the lung in adults is seldom diagnosed and is found in only a small percentage of autopsies. Internists and pathologists agree that the lungs of the adult are relatively immune to manifestations of the infection. A few authentic cases have been diagnosed and reported. The diagnosis should be confirmed by history, physical findings, laboratory and X-ray examinations, and response to anti-syphilitic treatment. There are no pathognomonic lesions. When lesions do occur they are usually late manifestations of the disease. Roentgenologically, three types may be described: (1) that showing generalized bronchial thickening and producing a fan shaped effect, (2) that showing solitary and multiple or solitary discrete masses, usually present near the root but also found at the periphery, and developing a delimiting zone of pneumonitis in the early stage, (3) a diffuse lobar form. The first type may be confused with malignant tumor, and in the early stage the second type may resemble lobular tuberculosis or lung abscess. Symptoms and signs may be absent or the patient may have all the complaints of active tuberculosis. Hemoptysis may be the first symptom. The author reports a case referred with a diagnosis of tuberculosis, but the patient undoubtedly had syphilis of the upper and lower lobes of the left lung. The lung cleared entirely after four treatments. Attention is called to the possibility of confusing such cases with tuberculosis or tumors of the lung—*Pulmonary Syphilis in Adults, with Report of a Case, W. W. Robinson, Rad. Clin., November, 1935, xxi, 596—(G. F. W.)*

**Recovery from Amyloidosis**—A thirty four year old man, giving a history of productive cough and fever of five months' duration, was found to have fibrocascous

tuberculosis of the entire right lung with a large cavity near the right hilum and an exudative infiltration of the left lung. Pneumothorax was induced on the right side. Two and a half months later a purulent effusion developed. The fluid contained tubercle bacilli and gram positive cocci. Two months later, in January, 1932, an empyema *necessitatis* perforated through the 5th intercostal space. On May 20, 1932, a thoracotomy was done, and after removing 3.8 litres of pus a rubber catheter was inserted to promote free drainage. By July the patient had begun to improve, and by January, 1933, he was afebrile. At the time of writing (May, 1935) the fluid had been completely resorbed from the right side of the chest, and there was only 0.5 cc of pus draining daily from the thoracotomy sinus. By July, 1932, nine months after the appearance of the empyema, amyloidosis had developed as evidenced by retention of congo-red (54 per cent), albuminuria, and hepatomegaly. In March, 1933, nine months after the patient had begun to improve clinically, and two months after he had become afebrile, the amyloidosis reached its peak. There was at this time 100 per cent retention of congo red. The patient was excreting 10 gm albumin in the urine daily. The serum albumin had fallen to 1.96 gm per 100 cc. There was a three-plus hepatomegaly, a two plus splenomegaly, and a two plus peripheral oedema. The clinical and laboratory findings from that time on showed gradual improvement of the amyloidosis, and by April, 1935, the retention of congo-red was only 10 per cent. The excretion of albumin was 1.75 gm daily. The serum proteins had returned to normal, and the above mentioned abnormal physical findings had disappeared. At no time was there evidence of impaired renal function. Although the patient was given liver therapy from the middle of 1933 to August, 1934, the regression of the amyloidosis is felt to be due to improvement in the tuberculosis.—*Recovery from Generalized Amyloidosis Secondary to Pulmonary Tuberculosis*, M. R. Rosenblatt, *Arch Int Med*, March, 1936, lxx, 562.—(C. L. D.)

**Haemoptysis in Trichiniasis**—The occurrence of pulmonary signs and symptoms in trichiniasis is fairly well known and a variety of pathological lesions of both lungs and bronchi has been described to account for them. In Minot and Rackemann's series 50 per cent of the patients showed pulmonary signs or symptoms. There were three with blood-tinged sputum. In 1860, Wunderlich reported a case of haemoptysis in a butcher, the first diagnosis being acute

tuberculosis but the later one trichiniasis. Kestner has described a pneumonia due to trichinae but his description of symptoms suggests infection. Spink and Augustine recently reviewed 35 cases, of which two had cough with bloody sputum. Askanazy experimentally found young trichinae in lungs causing embolization with bronchiolar and alveolar haemorrhage. Frothingham reported necropsy findings in a case which supported Askanazy's experimental work. Ordinarily, in the differential diagnosis of haemoptysis, trichiniasis is not considered, and many textbooks neglect to mention it. In view of the frequency of trichina infestation and the little attention paid to the possible occurrence of haemoptysis in association with it, three cases are here reported. In one case the diagnosis was definitely established by biopsy, in the others the history and clinical symptomatology left little room for doubt. It is of interest that, in the third case, the onset was with coryza, chills, malaise and cough, and that bronchial neoplasm and bronchiectasis were suspected, also, that eosinophilia was not reported until quite late. Failure to find trichinae in the sputum corresponds with other observations.—*Haemoptysis in Trichiniasis*, L. J. Goldwater, I. Steinberg, H. Most, & J. E. Connery, *New England J. M.*, October 31, 1935, cxxix, 749.—(A. P.)

**Prognosis of Early Pulmonary Tuberculosis**—The prognosis in any given case is difficult but should be attempted. Undue importance should not be attached to the extent of physical signs. Toxic symptoms are of greater importance, and their persistence after complete rest and nursing-care augurs a worse outlook than persistence of physical signs and disappearance of toxic phenomena. Gradual increase in severity of such symptoms is not favorable, and the previous state of the patient's health is a factor to be considered. Persistence or increase of toxic symptoms with little or no apparent impairment of lung tissue should suggest the possibility of extrapulmonary involvement. The genitourinary tract must be kept in mind. Death is most common between the ages of 20 and 25 years, greater in females between 15 and 30 and greater among males after 30 years. A general predisposition to the disease is probably transmitted from parent to child, and the prognosis of an individual of a family in which there had been deaths from tuberculosis would be more grave than normally. Prognosis in cases with insidious onset must be guided often by the response to proper treatment. The presence of healed areas in the lung makes it more favorable. When



the duration of symptoms is short and there is moderate destruction of lung tissue, bodily response must be assumed to be weak and the prognosis bad. A small unilateral lesion is favorable, and early involvement of both lungs denotes a bad outlook. Prognosis in the pneumonic type is unfavorable. It is usually believed that cases starting with haemoptysis are favorable, but bleeding should not be considered lightly, especially in a young adult. It should be assumed that it indicates pulmonary disease, in spite of possible negative evidence, and the prognosis will be influenced by this consideration. In onset with spontaneous pneumothorax, prognosis is difficult, but, lacking sufficient evidence and assuming a good contralateral lung, it is usually good. Very often, idiopathic pleurisy with effusion is followed a few years later by definite evidences of pulmonary disease. Laryngeal involvement is usually late. Prognosis is more serious when the larynx is involved and the lungs only slightly so. Prognosis will also be influenced by the treatment that is available and the patient's capacity to carry out such treatment, for to day we see cases with poor outlook make rapid improvement and go on to enjoy moderately good health when proper treatment has been carried out.—*The Prognosis of Early Pulmonary Tuberculosis*, J. B. Alexander, *J. State Med.*, July, 1936, *xlv*, 402 —(L. F. B.)

**Prognosis in Pulmonary Tuberculosis with Cavitation**—Until comparatively recently, cavity-formation in the course of pulmonary tuberculosis was regarded as a terminal and incurable stage. However, with adequate treatment, closure and restoration of a patient's working capacity are possible, and, in many cases, without resort to collapse therapy. Statistics published from Trudeau Sanatorium in 1931 noted that collapse therapy was applied only to those patients who, after a preliminary period of general treatment, failed to show satisfactory healing. McMahon and Kerper, at Loomis Sanatorium, found spontaneous closure in 22 per cent of 296 cases with cavitation and obliteration by collapse therapy in 34 per cent. Altogether, 39 per cent obtained closure and 25 per cent more were much improved. These figures are in striking contrast to those of Barnes and Barnes who, in a series of 1,454 cases with cavitation, found a mortality of 80 per cent within one year, and of Watt, with a smaller series not treated by collapse. The most probable explanation of the discrepancy is that the authors quoted have not differentiated between the various types of cavities at different stages of the disease. Jacquerod,

describes three stages in cavity development, beginning with a comparatively ill-defined circular shadow, passing through a second stage with a well-defined ring, and ending with the typical thick-walled cavity seen in the chronic case of some years' duration. Pottenger has pointed out that "the healing of early cavities depends primarily on the patient's ability to marshal an adequate defense, while the healing of a late cavity is primarily a mechanical problem—the fact that the disease has become chronic denotes resistance." Keers has studied the case-records from the Tor-na-Dee Sanatorium, Aberdeenshire, and analyzed 100 consecutive cases with cavitation from the end of 1924 until the beginning of 1930, their progress being followed to the end of 1932, at which time 49 were living and 51 dead. Of those living, 5 had bilateral cavitation, 22 on the right and 22 on the left. All but eight had bilateral disease. The basis of treatment was bed-rest and the usual hygienic-dietetic regimen, supplemented in suitable cases by collapse therapy, in 21 instances artificial pneumothorax. In only one third of the latter was collapse effective, and another one-third underwent other forms of collapse, usually phrenic evulsion, of whom 4 became arrested or improved, compared with 3 of 7 who had no subsequent procedures tried. A group of 28 regarded as unsuitable for collapse had general rest treatment, in some instances supplemented by sanocrysin or colloidal calcium. Of these, 13 achieved arrest. This term was applied to those able to lead a reasonably normal life and either sputum free or sputum-negative. Complete obliteration of the cavity was not necessarily required. Of patients who had died, 9 had bilateral excavation, 25 right and 17 left. Artificial pneumothorax was attempted in 11, and was not effective in any case. *Summary of results* 1 Artificial pneumothorax was applied in 24 cases (operative failures not included), of which 9 obtained arrest and 10 died. 2 Thoracoplasty was applied in 9 cases, of which 3 obtained arrest and 2 died. 3 Rest treatment alone was applied in 67 cases, of which 13 obtained arrest and 39 died. It does not appear that pneumothorax was more effective in the first stage cavities than in the more advanced ones. However, the sum total of cases obtaining arrest was much higher for first stage cavities (nearly 50 per cent) and lowest for third stage (less than 20 per cent). No fatal hemorrhages occurred with first-stage cavities, and 8 of 10 such were those in the third stage. *Conclusions* 1 The prognosis in cavity cases is closely related to the type of lesion. 2 When cavity is in the lower lobe the outlook is

serious unless it can be effectively dealt with by collapse. 5 Artificial pneumothorax has been unexpectedly disappointing, due mainly to pleural adhesions preventing effective collapse. The result would probably be improved by earlier application. 6 Phrenicectomy is of limited value in cases of excavation and in none of these was alone sufficient to obliterate cavities. 7 In carefully selected third-stage cases thoracoplasty is more likely to produce benefit than any of the other collapse procedures. 8 An uncollapsed cavity is a potential source of severe haemoptysis, and 20 per cent of deaths in this series were due to such cause.—*Contribution to Pulmonary Tuberculosis. A Review of One Hundred Cases, R. 7 Keers, Tubercle, December, 1935, pt. 1, 105*—(A. P.)

**Distribution and Prognosis of Pulmonary Lesions**—The lung field may be divided into six regions. Areas 1, 2 and 3, respectively, about equally divide the upper third of the lung, and are numbered from the mediastinum to the chest wall. Area 4, having an almost horizontal upper border and dipping in a salient to the diaphragm in the midthoracic line, comprises the middle third of the pulmonary cone. Area 5 is a cardiophrenic triangle, the lateral border of which extends from the hilum to the middle of the diaphragm. Area 6 is the costophrenic triangle left by area 5. Areas 1, 2 and 3 are typical sites of origin for adult type, while area 4 is the site for the childhood type tuberculosis. Severe lesions in area 4 are based on the posterior, and slighter ones on the anterior chest wall. Chronic nontuberculous bronchopneumonia at all ages almost invariably originates and has its maximum severity in the cardiophrenic angle, whence during exacerbations it spreads along the diaphragmatic contour. Such lesions are associated with persistently negative sputum and, in children, with tuberculin reactions consistently negative for years. In 51 cases sputum positive lesions of both childhood and adult types, that have become sputum negative with little or no treatment, have been observed in synchronized stereoscopic roentgenograms and in closely spaced multiangular views (the angle varying from 5 to 60 degrees depending on the silhouette). Two patients in the series were under 10, and 9 were over 45 years of age. The tuberculous lesion was classified as minimal in 13, as moderate in 24, and as far advanced in 14 cases, while the cardiophrenic lesions were severe in 31, marked in 15 and slight in 3 cases. These 51 cases were compared with cases of uncomplicated nontuberculous pulmonary lesions

and uncomplicated tuberculosis. It was found that tuberculous lesions (in areas 1, 2, 3 or 4), which were associated with active and persistent lesions in area 5, retrogressed rapidly, with contraction of cavities and disappearance of tubercle bacilli from the sputum. With complete arrest of the tuberculous lesions, the lesion in area 5 may fluctuate for years, with persistently negative sputum. On the other hand, in many clinic cases relapse of tuberculosis has followed healing of a lesion in area 5, during the acute stage of which the apical or childhood type lesion had retrogressed. Lesions that, according to the accepted classification, are far advanced because the greater part of the lung including area 5 is involved have had a more favorable course than lesions of lesser extent and severity which are confined to the upper two thirds of the lung field or have invaded area 5 only in terminal stages.—*The Distribution and Prognosis of Pulmonary Lesions Associated Tuberculois and Nontuberculous, I. M. McPhedran, Am. J. M. Sc., December, 1935, xxx, 659*—(E. M. J.)

**Clinical Estimation of Resistance**—Close observation and long acquaintance with tuberculosis, supplemented by sound clinical background and a knowledge of pathology, can usually justify a fairly accurate prognosis. Among factors to be considered are (1) history and mode of onset—cases with febrile onset or following debilitating disease are least favorable, pleurisy is chiefly important as regards the feasibility of pneumothorax therapy, obliterative adhesions being the rule, the poor have an advantage over the rich in the degree of revolution in their mode of life while under treatment, but a disadvantage in the facilities for continuing this, the family history is important chiefly in discovering the degree and length of possible exposure. (2) general appearance and personal estimate—intelligent inspection of the stricken patient is most important, for loss of muscle tone, myotonic irritability or wasting, tendency to sweating, color of skin and nail beds, are all important indications of the constitutional effects of the disease, and the state of nutrition should be noted, while an estimate of temperament or personality is highly important and (3) physical and X-ray findings which should complement each other and each be done carefully and completely, for to neglect either is futile, the X-ray film will show better the early, clinically silent, thin walled cavity and distinguish it from the more serious thick walled long standing vomica, and, by indicating the full extent of contralateral involvement, it will help settle the important question of collapse

therapy The quantitative tuberculin test is probably of no significant prognostic value Serum flocculation tests, such as the Vernes, may be of value, the technique is simple, and the error due to personal equation small Valuable are the erythrocyte sedimentation rate, repeated at intervals, and blood film examinations The rapidity of red-cell sedimentation is particularly an index of tissue disturbance or protein disintegration Stained blood films may be useful for classifying the neutrophilic leucocytes or for determining the percentage ratio of lymphocytes, monocytes and neutrophils, this information that should be regarded as merely suggestive or supplementary The estimation of vital capacity is a further functional test, while the determination of type of tubercle bacillus is more of academic than practical interest—*Remarks on the Clinical Estimation of Resistance in Pulmonary Tuberculosis*, D P Marais, *British J Tuberc*, April, 1936, xxx, 72—(1 P)

**X-Ray in Prognosis of Tuberculosis**—From a study of selected groups of several hundred consecutive admissions to Trudeau Sanatorium, and following the patients in each group for some years, the following conclusions are drawn The extent of pulmonary involvement greatly influences the prognosis in pulmonary tuberculosis, the death rate being in direct proportion to the amount of disease The presence of cavities nearly doubles the probability of death within five years Cavity cases showing improvement under treatment have approximately five times as favorable a prognosis as those in which the cavities become larger during sanatorium residence Patients whose comparative roentgen examinations are constantly favorable under sanatorium treatment have more than twice as good a chance of being well at the end of a five-year period and only one fourth as a great a chance of being dead as those who have increased X ray shadows Increase of infiltration in comparative X ray studies suggests a prognosis about equally unfavorable with that indicated by the presence of fever Patients with both fever and increased X ray shadows have six times as unfavorable an outlook as those who are afebrile and who show consistent roentgenographic improvement Increased comparative X ray shadows are of much graver prognostic significance than increased physical signs (râles)—*Use of the X-Rays in Pulmonary Tuberculosis from the Point of View of Prognosis*, F B Trudeau, *J Am M Assn*, February 22, 1936, cvi, 592—(G L L)

**Red-Cell Sedimentation and Blood Viscosity**—The viscosity of the whole blood, and not that of the plasma alone, determines the sedimentation rate of blood cells This viscosity is influenced by a large number of factors Among these Einstein's formula expresses some of the important factors  $N = N^0 (1 + 2.5V)$ , where  $N$  is the viscosity of the suspension,  $N^0$  the viscosity of the fluid medium, and  $V$  the volume occupied by the particles in suspension It results from this that a reduction in the number of red cells in the blood will reduce viscosity of the blood, and hence increase the sedimentation rate An increase in the volume of the individual corpuscles without any increase in number will also increase the viscosity of the blood, and delay sedimentation The viscosity of the plasma itself is primarily determined by the protein in solution and especially by the ratio existing between the different proteins in solution An increase in the relative concentration of the large molecules such as the globulins at the expense of the albumins, will reduce the viscosity of the plasma due to the relatively smaller number of globulin molecules in the plasma in relation to the number of the smaller molecules of albumin, crystalloids in solution exert little influence on blood viscosity and hence on the sedimentation rate—*Séminatoire globulaire et viscosité sanguine*, M Berrot Re Libere, February, 1936, ii, 152—(M B I)

**Vaccination against Tuberculosis**—There is much experimental evidence in favor of the viewpoint that previous contact with tubercle bacilli produces a certain immunity to tuberculosis In guinea pigs, appropriate previous injections with virulent human or bovine tubercle bacilli given intracutaneously, subcutaneously or intravenously, retard the development of subsequent infection with virulent human or bovine tubercle bacilli Avirulent human strains of tubercle bacilli have never before been tested in viable form on man The human beings used in the test showed no clinical evidence of tuberculosis or other diseases They were given intracutaneous tests of purified tubercle protein to determine their relative tuberculin reacting power The subjects were thus grouped as being relatively tuberculin negative or positive, and given avirulent human or bovine tubercle bacilli intracutaneously Whether the bacilli were viable or not (heat or chemically killed) or whether they were virulent human or bovine tubercle bacilli, the intracutaneous lesions produced with concentrations ranging from 0.001 mgm of bacilli in fine suspension

